THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 144, Number 3 March 1987

In this issue:

Intensive Psychodynamic Therapy With Borderline Patients: An Overview

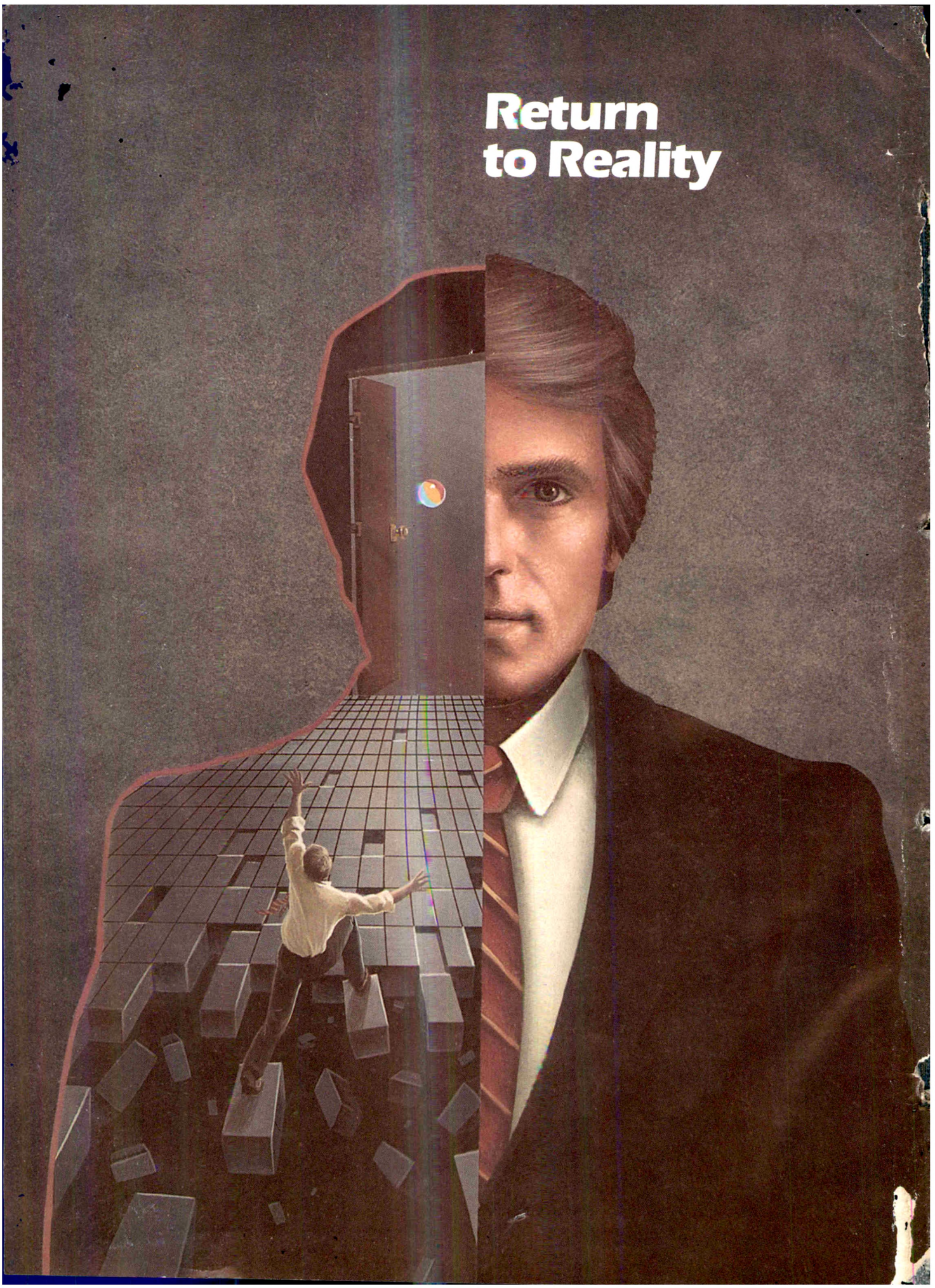
By Robert J. Waldinger

Control Groups for Psychosocial Intervention Outcome Studies

By Joseph M. Strayhorn, Jr.

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Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias; bone marrow depression; liver damage.

Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. (See PRECAUTIONS.)

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, hemolytic anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent in vitro, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., mitral insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecomastia, false positive pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema, reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

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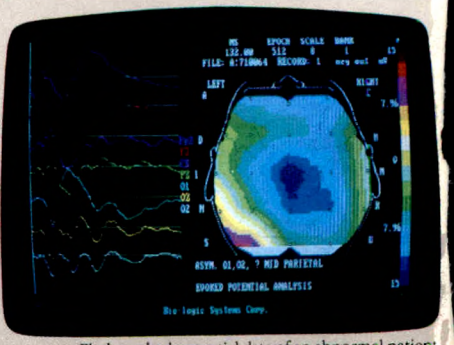
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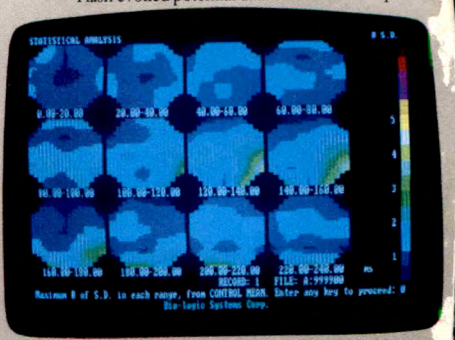
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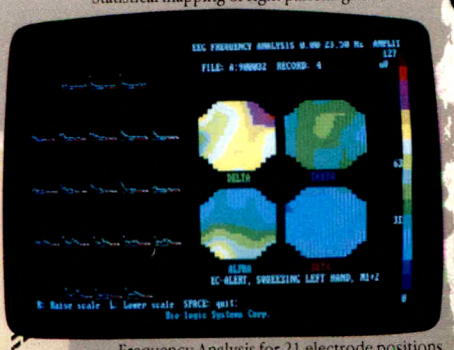
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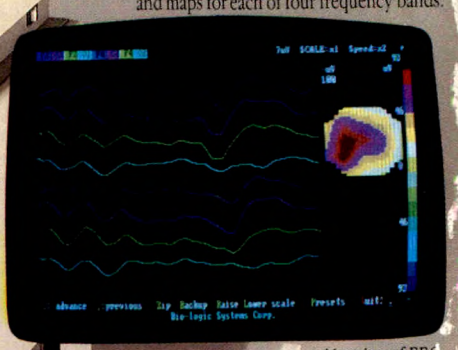
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The American Journal of Psychiatry, ISSN 0002-953X, is published monthly by the American Psychiatric Association, 1400 K Street, N.W., Washington, DC 20005. Subscriptions: U.S. $50.00 per year, Canada and foreign $65.00; single issues: U.S. $7.00, Canada and foreign $8.00.

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Business Management: Nancy Frey, Director, Periodicals Services; Laura G. Abedi, Advertising Production Manager: (202) 682-6154; Beth Prester, Director, Circulation; Karen Loper, Promotion Manager; Jackie Coleman, Fulfillment Manager.

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Type set by Byrd PrePress, 5408 Port Royal Road, Springfield, VA 22151. Printed by Dartmouth Printing Company, 69 Lyme Road, Hanover, NH 03755.

Second-class postage paid at Washington, DC, and additional mailing offices. POSTMASTER: Send address changes to Circulation Department, American Psychiatric Association, 1400 K Street, N.W., Washington, DC 20005.

Indexed in *Abstracts for Social Workers, Biological Abstracts, Chemical Abstracts, Chicago Psychoanalytic Literature Index, Cumulative Index to Nursing Literature, Excerpta Medica, Hospital Literature Index, Index Medicus, International Nursing Index, Nutrition Abstracts, Psychological Abstracts, Science Citation Index,* and *Social Sciences Index.*

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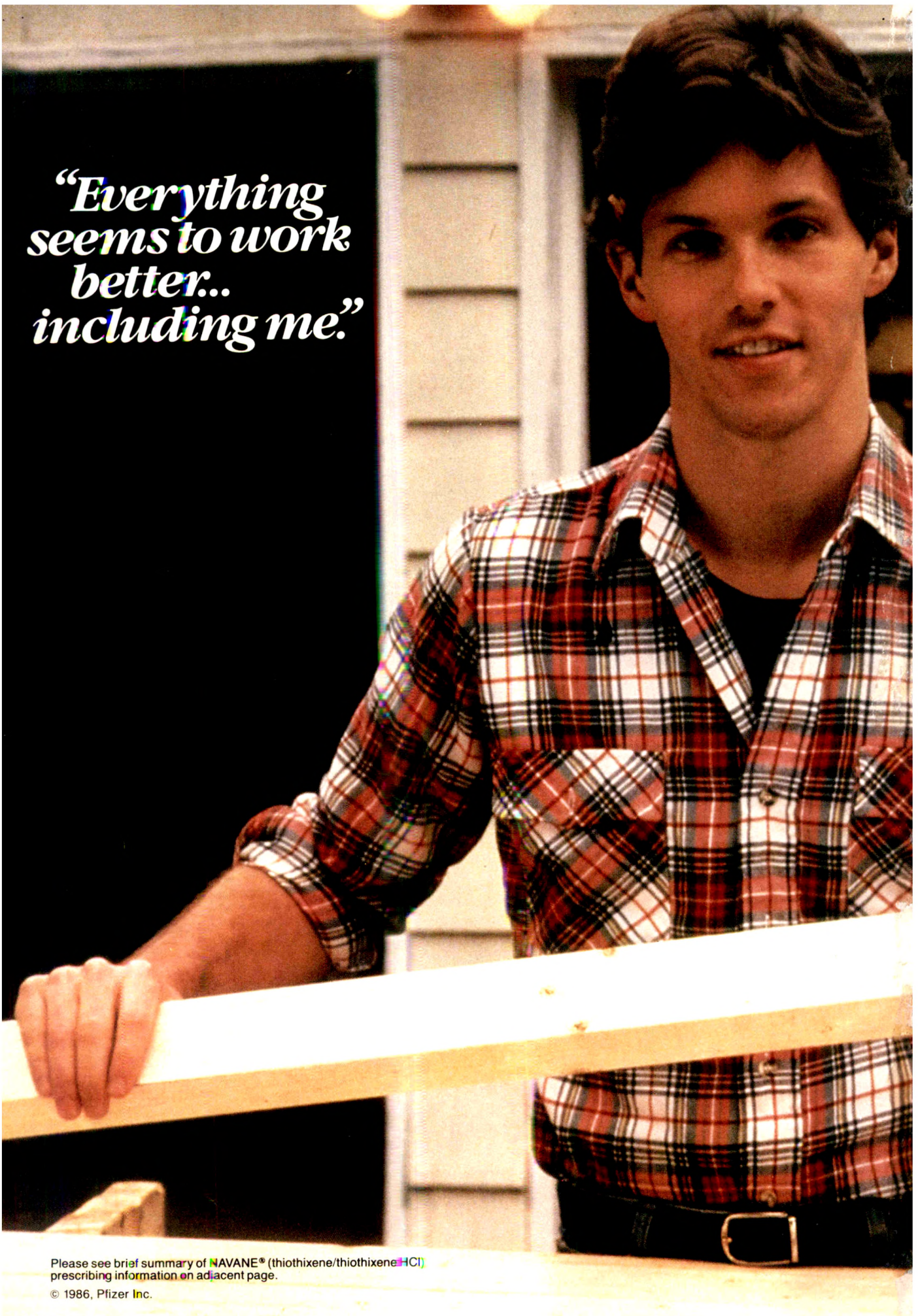
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References: **1** Bressler B, Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. **2** DiMascio A, Demirgian E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. **3** DiMascio A, Demirgian E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association, Washington, DC, May 3-6, 1971. **4** Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients, in Lehmann HE, Ban TA (eds): *The Thioxanthenes: Modern Problems of Pharmacopsychiatry*. Basel, Switzerland, S Karger, 1969, vol 2, pp 45-52. **5** Dillenkofer RL, Gallant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented as a Scientific Exhibit at The 125th Annual Meeting of The American Psychiatric Association, Dallas, May 1-4, 1972. **6** Data available on request from Roerig.

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Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treament, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the section on Adverse Reactions.)

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long term therapy or may occur after drug therapy has been discontinued. The risk seems to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage and Administration: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. In general, small doses should be used initially and gradually increased to the optimal effective level, based on patient response.

Some patients have been successfully maintained on once-a-day Navane therapy.

Usage in children under 12 years of age is not recommended because safe conditions for its use have not been established.

Navane Intramuscular Solution: Navane For Injection—When more rapid control and treatment of acute behavior is desirable, the intramuscular form of Navane may be indicated. It is also of benefit where the very nature of the patient's symptomatology, whether acute or chronic, renders oral administration impractical or even impossible.

For treatment of acute symptomatology or in patients unable or unwilling to take oral medication, the usual dose is 4 mg of Navane Intramuscular administered 2 to 4 times daily. Dosage may be increased or decreased depending on response. Most patients are controlled on a total daily dosage of 16 to 20 mg. The maximum recommended dosage is 30 mg/day. An oral form should supplant the injectable form as soon as possible. It may be necessary to adjust the dosage when changing from the intramuscular to oral dosage forms. Dosage recommendations for Navane (thiothixene) Capsules and Concentrate appear in the following paragraphs.

Navane Capsules; Navane Concentrate—In milder conditions, an initial dose of 2 mg three times daily. If indicated, a subsequent increase to 15 mg/day total daily dose is often effective.

In more severe conditions, an initial dose of 5 mg twice daily.

The usual optimal dose is 20 to 30 mg daily. If indicated, an increase to 60 mg/day total daily dose is often effective. Exceeding a total daily dose of 60 mg rarely increases the beneficial response.

Overdosage: Manifestations include muscular twitching, drowsiness, and dizziness. Symptoms of gross overdosage may include CNS depression, rigidity, weakness, torticollis, tremor, salivation, dysphagia, hypotension, disturbances of gait, or coma.

Treatment: Essentially is symptomatic and supportive. For Navane oral, early gastric lavage is helpful. For Navane oral and intramuscular, keep patient under careful observation and maintain an open airway, since involvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overdosage. If hypotension occurs, the standard measures for managing circulatory shock should be used (I.V. fluids and/or vasoconstrictors.)

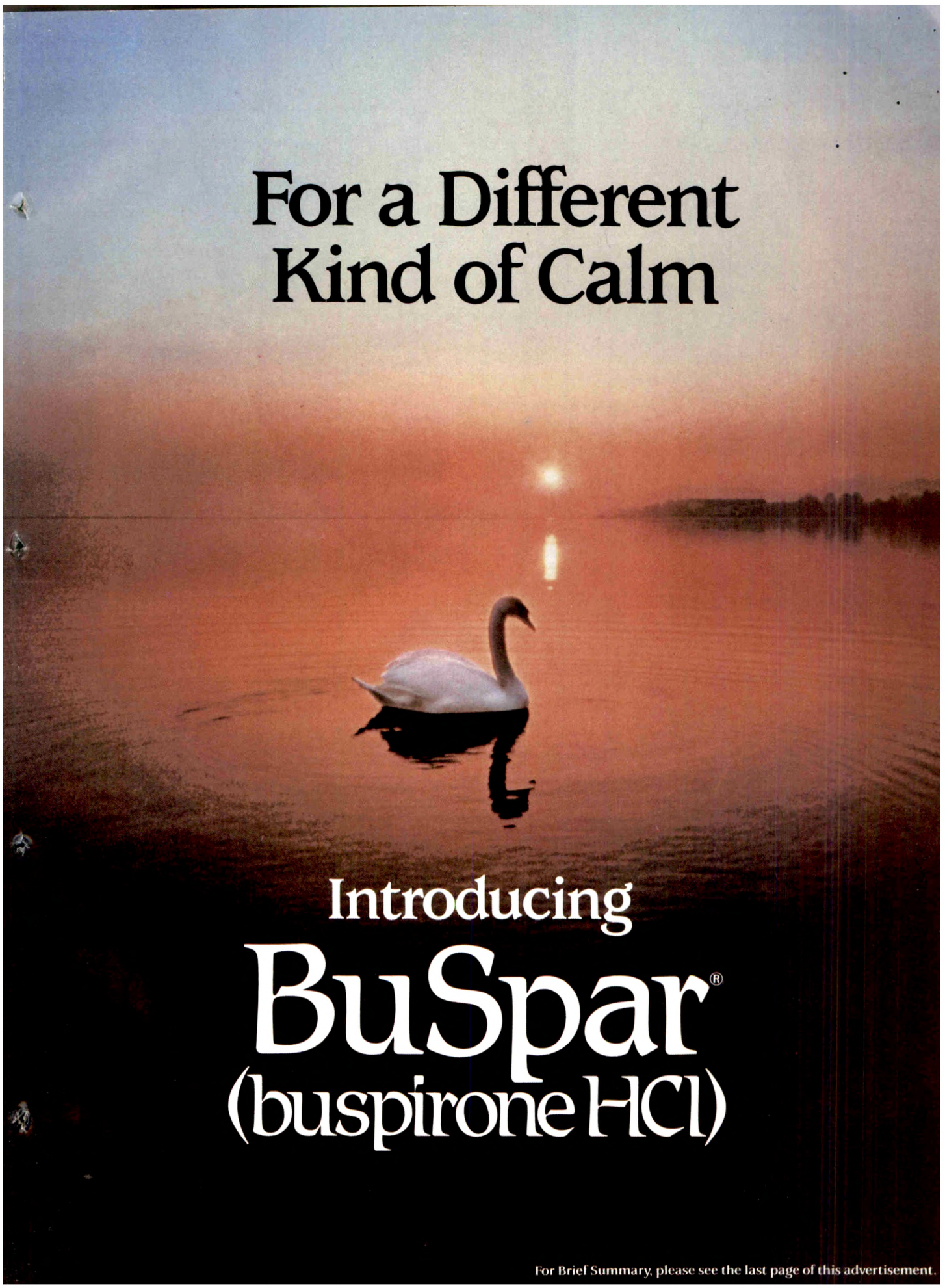
If a vasoconstrictor is needed, levarterenol and phenylephrine are the most suitable drugs. Other pressor agents, including epinephrine, are not recommended, since phenothiazine derivatives may reverse the usual pressor action of these agents and cause further lowering of the blood pressure.

If CNS depression is present and specific therapy is indicated, recommended stimulants include amphetamine, dextroamphetamine, or caffeine and sodium benzoate. Stimulants that may cause convulsions (e.g. picrotoxin or pentylenetetrazol) should be avoided. Extrapyramidal symptoms may be treated with antiparkinson drugs.

There are no data on the use of peritoneal or hemodialysis, but they are known to be of little value in phenothiazine intoxication.

ROERIG Pfizer

A division of Pfizer Pharmaceuticals
New York, New York 10017


For a Different
Kind of Calm
Introducing
BuSpar®
(buspirone HCl)
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Mead Johnson
Pharmaceutical Division
Introduces

NEW

BuSpar®

Tablets
5 mg and 10 mg

(buspirone HCl)

A different kind of calm

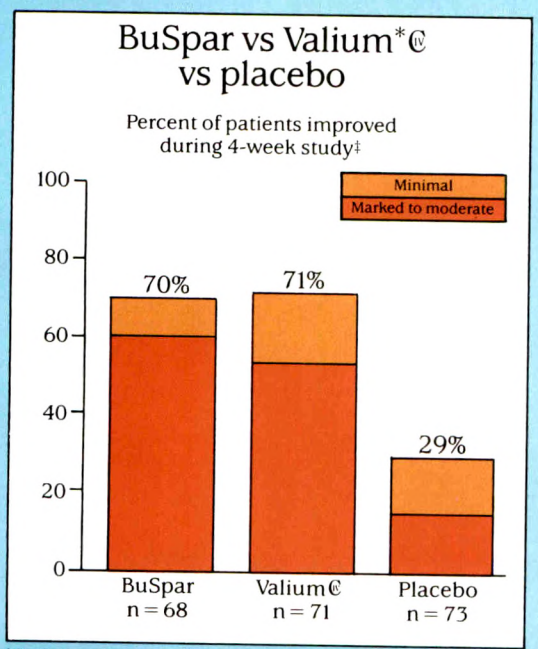
BuSpar—the first anxiolytic without CNS-depressant activity—has broken the connection between efficacy and unwanted sedative effects.

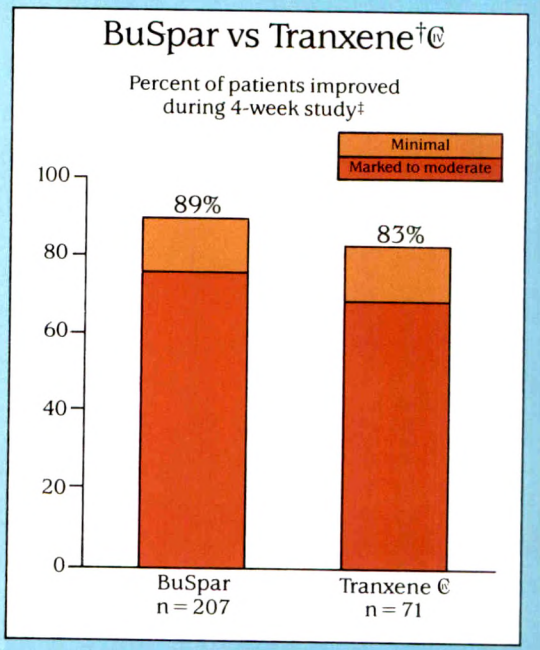
BuSpar gradually and comfortably provides relief of anxious symptoms—but produces no more drowsiness, motor impairment, or interaction with alcohol than does placebo.[2,3]

Furthermore, in clinical studies, BuSpar exhibited no apparent abuse liability, and no withdrawal syndrome has been reported at the end of therapy.[4,5]

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Proven anxiolytic effectiveness over a 4-week course of therapy[6,7]





*Registered trademark of Hoffmann-La Roche Inc for diazepam.
†Registered trademark of Abbott Pharmaceuticals, Inc for clorazepate.
‡Physician's assessment of global improvement.

Extensive clinical trials have shown that BuSpar produces impressive results over a four-week course of therapy. In comparative trials with Valium and Tranxene, 70% to 89% of patients receiving BuSpar were judged by their physicians to be improved at the end of therapy. Significant improvement was noted in a wide range of anxiety-related symptoms such as anxious mood, depressed mood, and cardiovascular and gastrointestinal complaints.

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NEW

BuSpar®

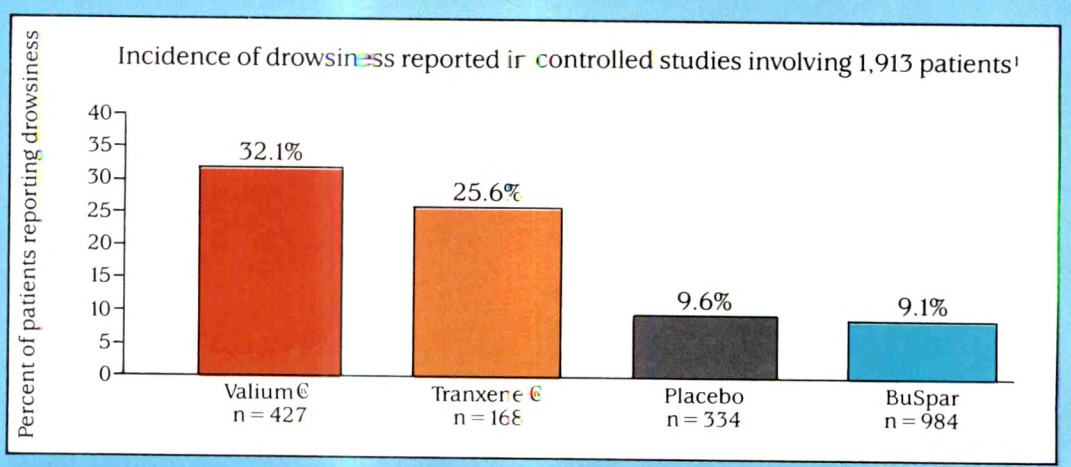
Tablets
5 mg and 10 mg

(buspirone HCl)

Anxiolytic efficacy without CNS-depressant activity

Incidence of drowsiness no greater than placebo

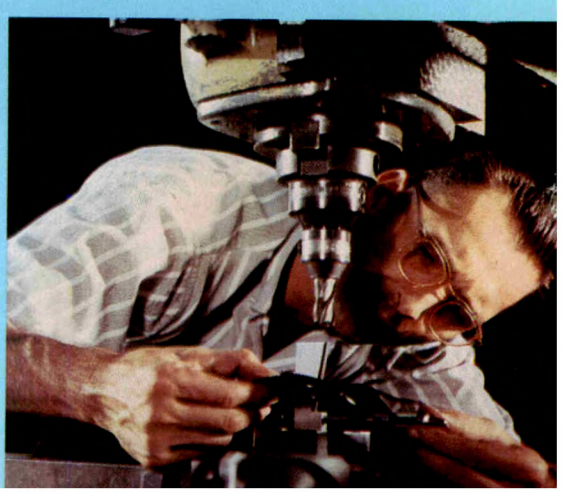
Because BuSpar does not replace symptoms with sedation, patients are alert and aware as well as anxiety-free during their waking hours.[1]



No impairment of motor skills

Controlled studies show that, unlike diazepam, BuSpar did not interfere with driving skills in normal subjects.[2]

NOTE: Patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.





No potentiation of the effects of alcohol

Controlled studies in normal subjects showed that, unlike lorazepam, BuSpar did not augment the effects of alcohol.*[3]

No apparent abuse liability

Extensive preclinical information and clinical data from studies in two populations, recreational users of sedatives and alcohol-dependent patients, demonstrate that BuSpar does not have the characteristics of common substances of abuse. Therefore, BuSpar is not a controlled substance.[4,8]

Well tolerated...with a low incidence of troublesome side effects

The most commonly observed adverse effects in controlled trials were dizziness (12%), nausea (8%), headache (6%), nervousness (5%), light-headedness (3%), and excitement (2%).

*While formal studies of the interaction of BuSpar with alcohol indicate that BuSpar does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and BuSpar.

For Brief Summary, please see the last page of this advertisement.



NEW

BuSpar®

Tablets
5 mg and 10 mg

(buspirone HCl)

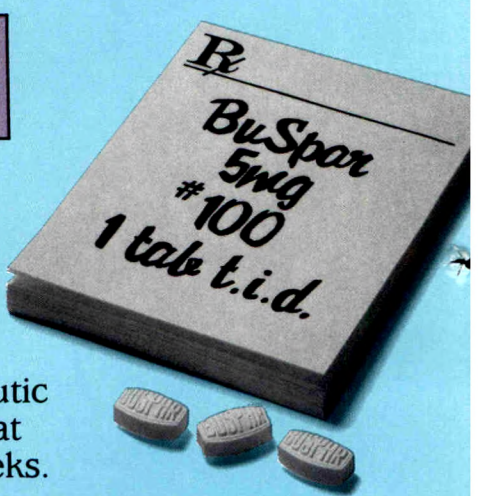
Subtle onset of effect

BuSpar relieves the symptoms of anxiety gradually and steadily. Generally, improvement will be noticeable within 7-10 days.

Prescribing recommendations

Initial dosage—5 mg t.i.d.

Week 1	5 mg	5 mg	5 mg



Dosage adjustment—5 mg/day increments, every 2-3 days, as needed, up to 60 mg/day.

Optimal daily dose—20-30 mg in divided doses, in most patients.

Length of therapy—To achieve full therapeutic benefit from BuSpar, it is recommended that treatment be prescribed for at least 3-4 weeks.

At the end of therapy

BuSpar therapy may be discontinued by simply stopping administration.

BuSpar is <u>not</u> a controlled substance.

Patient selection

BuSpar will <u>not</u> block benzodiazepine withdrawal syndrome... therefore, the best candidates for BuSpar are those not currently taking benzodiazepines.

If you elect to switch a patient from a CNS-depressant drug to BuSpar:

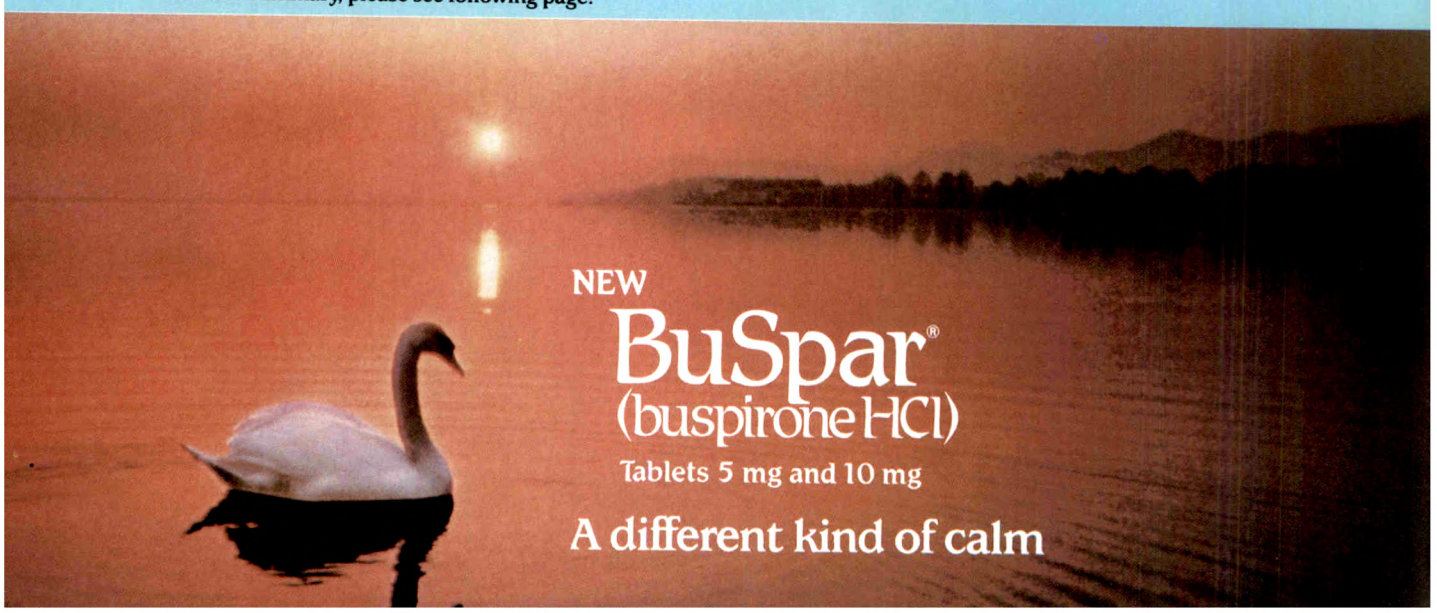
- Withdraw patients gradually from their prior treatment, especially those who have been using a CNS-depressant drug chronically.
- Recognize that rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its effective half-life of elimination.
- Remember that the withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

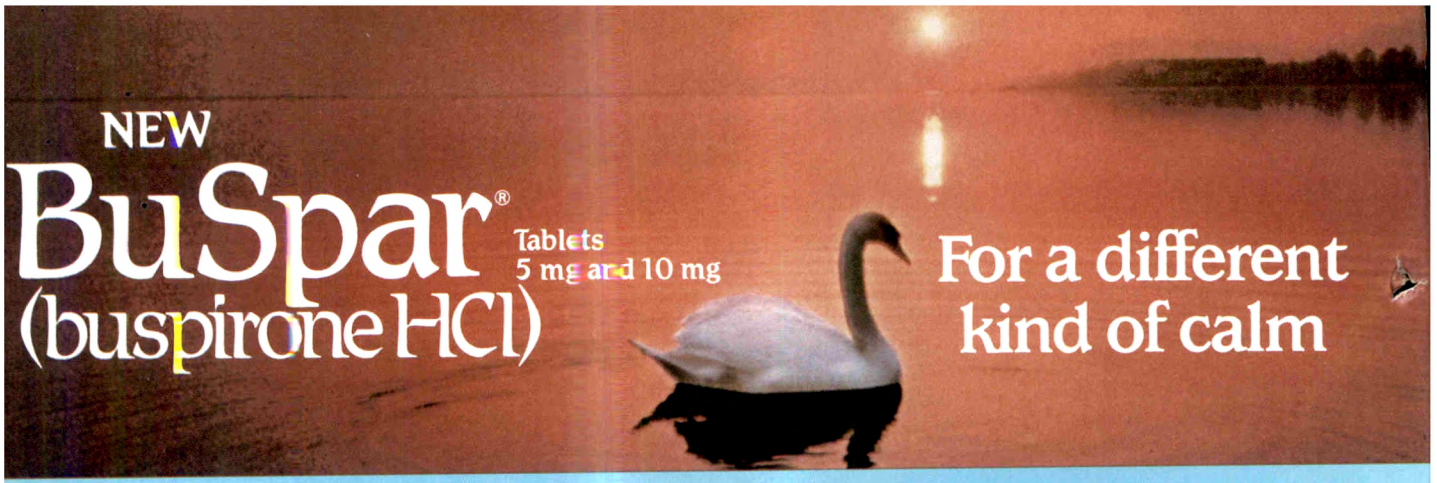
BuSpar therapy may be discontinued by simply stopping administration

BuSpar...the first choice in anxiolytic therapy when:

- ☑ Treatment requires regular dosing for more than a few days
- ☑ Patient functioning is key to safe and successful treatment
- ☑ The potential for drug habituation, dependence, abuse, or a withdrawal syndrome is a concern

For Brief Summary, please see following page.





CONTRAINDICATIONS:
Hypersensitivity to buspirone.

WARNINGS:
Because BuSpar has no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.

PRECAUTIONS:
General—
Interference with cognitive and motor performance:
Studies indicate that BuSpar is less sedating than other anxiolytics and that it does not produce significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely.

While formal studies of the interaction of BuSpar with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug-dependent patients:
Because BuSpar does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with BuSpar, it is advisable to withdraw patients gradually, especially patients who have been using a CNS depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug, and its effective half-life of elimination.

The syndrome of withdrawal from sedative/hypnotic/anxiolytic drugs can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors:
Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported in some small fraction of buspirone-treated patients. The syndrome may be explained in several ways. For example, buspirone may increase central noradrenergic activity; alternatively, the effect may be attributable to dopaminergic effects (i.e., represent akathisia). Obviously, the question cannot be totally resolved at this point in time. Generally, long-term sequelae of any drug's use can be identified only after several years of marketing.

Information for Patients:
Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions:
Concomitant use with other CNS active drugs should be approached with caution. There is one report suggesting that the concomitant use of Desyrel® (trazodone) and BuSpar may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. In a similar study, attempting to replicate this finding, no interactive effect on hepatic transaminases was identified. Buspirone does not displace tightly bound drugs like phenytoin, propranolol and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy:
Teratogenic Effects:
Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers:
Administration to nursing women should be avoided if clinically possible.

Pediatric Use:
The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly:
No unusual adverse age-related phenomena have been identified in elderly patients.

Use in Patients with Impaired Hepatic or Renal Function:
Since buspirone is metabolized by the liver and excreted by the kidneys, its administration to patients with severe hepatic or renal impairment cannot be recommended.

ADVERSE REACTIONS (See also Precautions):
Commonly Observed:
The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness, nausea, headache, nervousness, light-headedness and excitement.

Associated with Discontinuation of Treatment:
The more common events causing discontinuation included central nervous system disturbances (3.4%)—primarily dizziness, insomnia, nervousness, drowsiness, and light-headed feeling; gastrointestinal disturbances (1.2%)—primarily nausea; and miscellaneous disturbances (1.1%)—primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials:
Adverse events that occurred at a frequency of 1% or more among 477 patients who received buspirone in four-week, controlled trials: **Cardiovascular:** tachycardia/palpitations 1%. **CNS:** dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, light-headedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. **EENT:** blurred vision 2%. **Gastrointestinal:** nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. **Musculoskeletal:** musculoskeletal aches/pains 1%. **Neurological:** numbness 2%, paresthesia 1%, incoordination 1%, tremor <1%. **Skin:** skin rash 1%. **Miscellaneous:** headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Pre-Marketing Evaluation:
The following list includes all other adverse events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under various conditions in well-controlled studies as well as open and uncontrolled clinical settings. The relative frequency of these adverse events is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. **Cardiovascular:** Frequent was nonspecific chest pain; infrequent were syncope, hypotension and hypertension; rare were cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy and bradycardia. **Central Nervous System:** Frequent were dream disturbances; infrequent were depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, disassociative reaction, hallucinations, suicidal ideation and seizures; rare were feelings of claustrophobia, cold intolerance, stupor, and slurred speech and psychosis. **EENT:** Frequent were tinnitus, sore throat and nasal congestion. Infrequent were redness and itching of the eyes, altered taste, altered smell, and conjunctivitis; rare were inner ear abnormality, eye pain, photophobia, and pressure on eyes. **Endocrine:** Rare were galactorrhea and thyroid abnormality. **Gastrointestinal:** Infrequent were flatulence, anorexia, increased appetite, salivation, irritable colon and rectal bleeding; rare was burning of the tongue. **Genitourinary:** Infrequent were urinary frequency, urinary hesitancy, menstrual irregularity and spotting, and dysuria; rare were amenorrhea, pelvic inflammatory disease, enuresis and nocturia. **Musculoskeletal:** Infrequent were muscle cramps, muscle spasms, rigid/stiff muscles, and arthralgias. **Neurological:** Infrequent were involuntary movements and slowed reaction time; rare was muscle weakness. **Respiratory:** Infrequent were hyperventilation, shortness of breath and chest congestion; rare was epistaxis. **Sexual Function:** Infrequent were decreased or increased libido; rare were delayed ejaculation and impotence. **Skin:** Infrequent were edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema and blisters; rare were acne and thinning of nails. **Clinical Laboratory:** Infrequent were increases in hepatic aminotransferases (SGOT, SGPT); rare were eosinophilia, leukopenia and thrombocytopenia. **Miscellaneous:** Infrequent were weight gain, fever, roaring sensation in the head, weight loss and malaise; rare were alcohol abuse, bleeding disturbance, loss of voice and hiccoughs.

DRUG ABUSE AND DEPENDENCE:
Controlled Substance Class:
BuSpar is not a controlled substance.

Physical and Psychological Dependence:
Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE:
Signs and Symptoms:
No deaths have been reported in humans either with deliberate or accidental overdosage. At doses approaching 375 mg/day, the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress.

Recommended Overdose Treatment:
General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceutical Division Representative.

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May 6–10, annual meeting, American Psychoanalytic Association, Chicago. Contact Helen Fischer, Administrative Director, 309 East 49th St., New York, NY 10017; 212-752-0450.

May 6–10, annual meeting, Society of Biological Psychiatry, Chicago. Contact Philip A. Berger, M.D., Secretary-Treasurer, Dept. of Psychiatry, Stanford University School of Medicine, Stanford, CA 94305; 415-723-0852.

May 7–10, annual meeting, American Academy of Psychoanalysis, Chicago. Contact Vivian Mendelsohn, Executive Director, 30 East 40th St., Suite 608, New York, NY 10016; 212-679-4105.

May 8–10, annual meeting, American Society for Adolescent Psychiatry, Chicago. Contact Mary D. Staples, Executive Director, 24 Green Valley Rd., Wallingford, PA 19086; 215-566-1054.

May 9, annual meeting, American College of Psychoanalysts, Chicago. Contact Leo Madow, M.D., Secretary General, Institute of Pennsylvania Hospital, 111 North 49th St., Philadelphia, PA 19139; 215-471-2339.

May 9, annual meeting, American Society of Psychoanalytic Physicians, Chicago. Contact Mrs. Deborah C. Skolnik, Executive Director, 904 Dryden St., Silver Spring, MD 20901; 301-681-7385.

May 9–15, annual meeting, American Psychiatric Association, Chicago. Contact Cathy Earnest, APA, 1400 K St., N.W., Washington, DC 20005; 202-682-6237.

May 9–15, annual meeting, Christian Medical Society, Psychiatry Section, Chicago. Contact R. Bronson Stilwell, M.D., President, 4171 Crossover Rd., "E", Fayetteville, AR 72701; 501-521-5076.

May 10, annual meeting, American Association of Community Mental Health Center Psychiatrists, Chicago. Contact Gordon H. Clark, Jr., M.D., President, 88 Gale Ave., Laconia, NH 03246; 603-524-1255.

May 11, Diagnosis and Treatment of Depression: Quo Vadis? Sanofi Recherche, Montpellier, France. Contact Scientific Secretariat, Dr. Perla Roset-Danan, Centre de Recherches CLIN-MIDY/SANOFI, Rue du Pr. J. Blayac, 34082 Montpellier Cedex, France; 67-40-01-33; Telex 480 240.

May 11—15, annual meeting, Royal Australian and New Zealand College of Psychiatrists, Auckland, New Zealand. Contact Administrative Secretary, 101 Rathdowne St., Carlton 3053, Victoria, Australia; 03-663-5466.

May 14–17, annual meeting, American Geriatrics Society, New Orleans. Contact Linda Hiddeman Barondess, Executive Vice-President, 10 Columbus Circle, Suite 1470, New York, NY 10019; 212-582-1333.

May 16, annual meeting, Recovery, Incorporated (Association of Nervous and Former Mental Patients), Chicago. Contact Robert L. Farwell, Executive Director, 802 North Dearborn St., Chicago, IL 60610; 312-337-5661.

May 24–27, annual meeting, Association for the Care of Children's Health, Halifax, Nova Scotia, Canada. Contact Beverly H. Johnson, R.N., B.S.N., Executive Director, 3615 Wisconsin Ave., N.W., Washington, DC 20016; 202-244-1801.

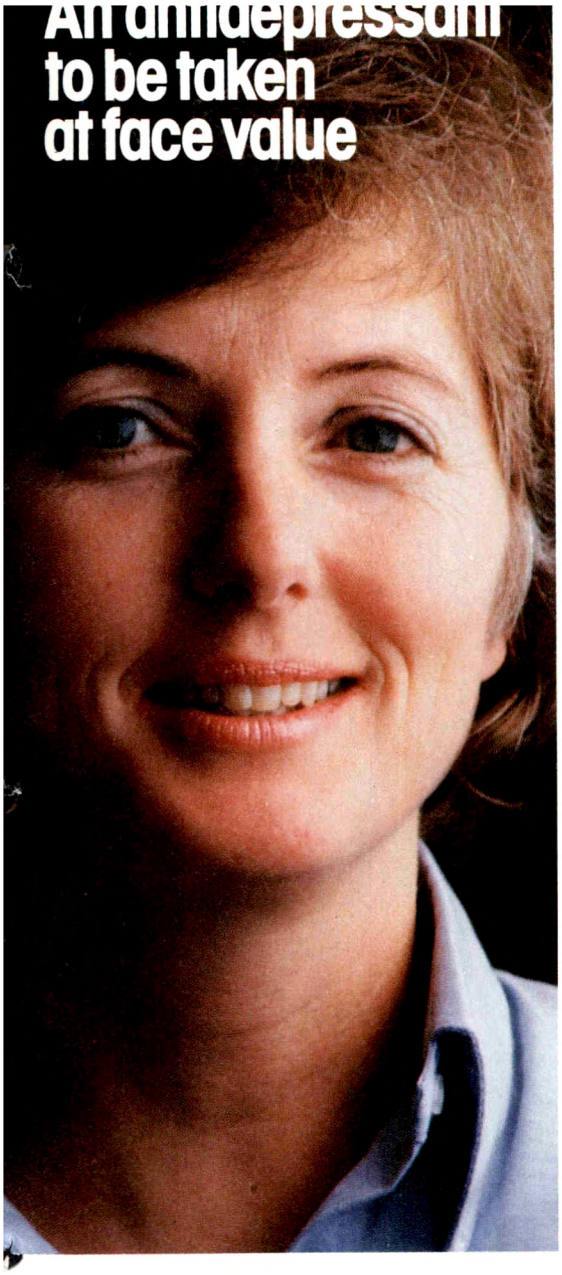
May 24–28, annual meeting, American Association on Mental Deficiency, Los Angeles. Contact Albert J. Berkowitz, Ed.D., Executive Director, 1719 Kalorama Rd., N.W., Washington, DC 20009; 202-387-1968.

May 25–30, annual meeting, American Association of Suicidology, San Francisco. Contact Julie Perlman, M.S.W., Executive Officer, 2459 South Ash, Denver, CO 80222; 303-692-0985.

May 27–30, annual meeting, American College Health Association, Chicago. Contact Stephen D. Blom, Executive Director, 15879 Crabbs Branch Way, Rockville, MD 20855; 301-963-1100.

May 29–June 1, annual meeting, International Physicians for the Prevention of Nuclear War, Inc., Moscow. Contact Thomas C. Chalmers, M.D., Research Program Chairman, IPPNW, 225 Longwood Ave., Boston, MA 02115; 617-738-9404; Telex 4430017 IPPNW.

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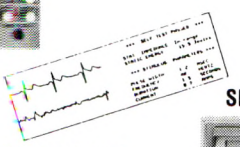


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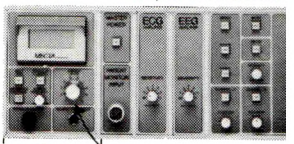


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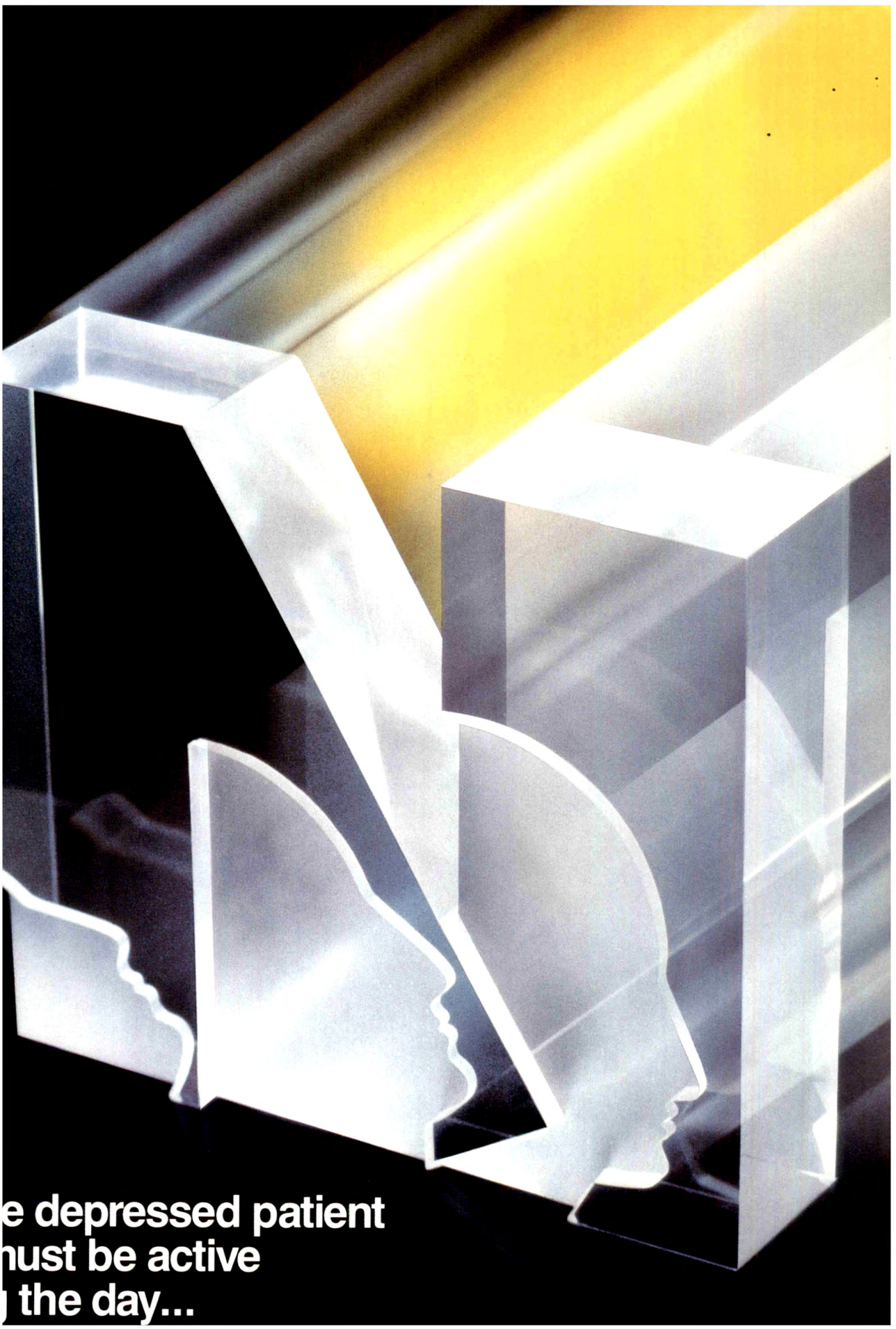
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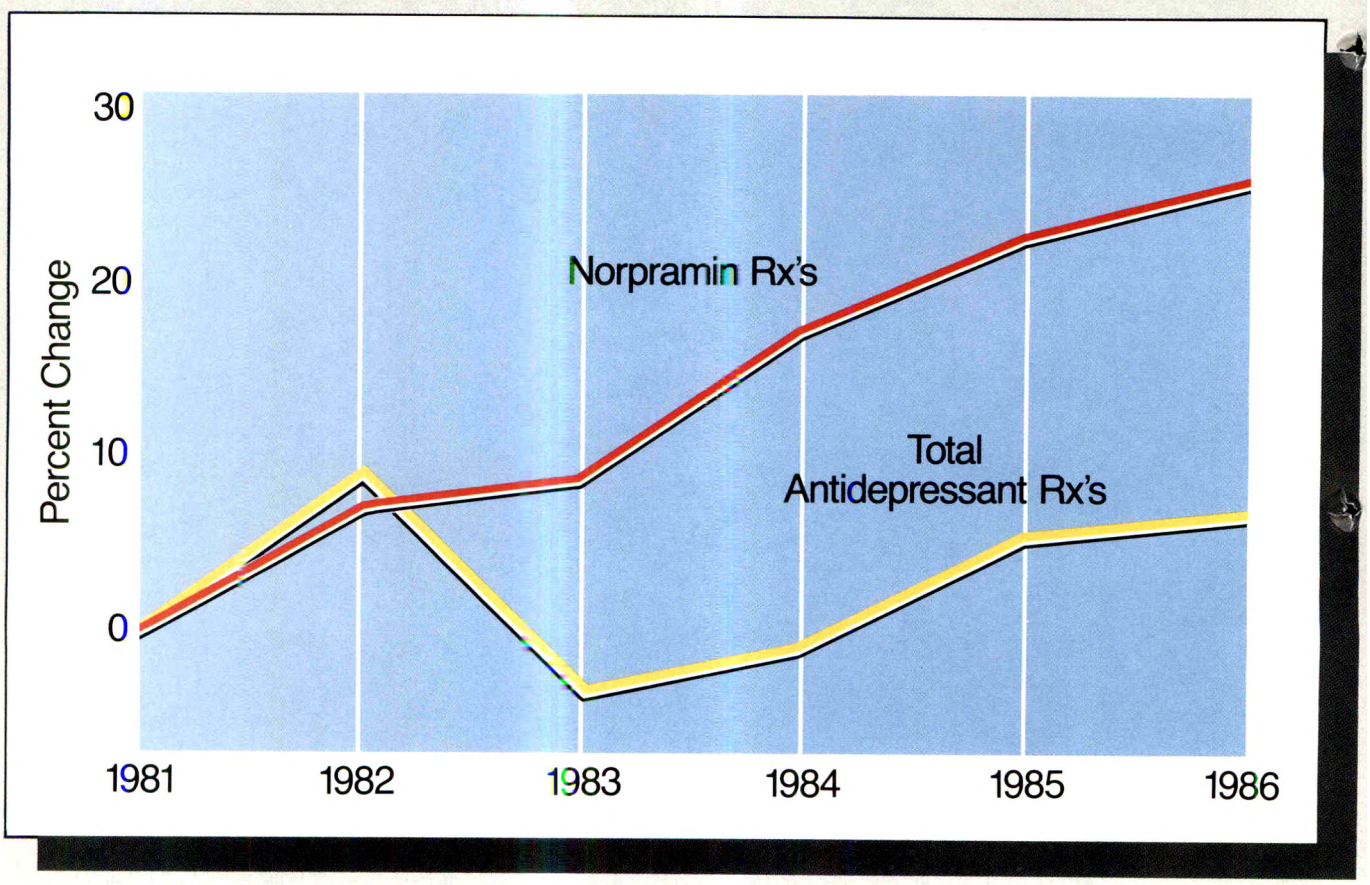


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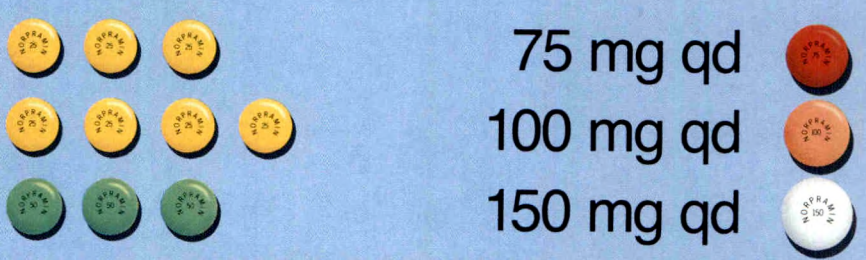
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MECHANISM OF ACTION: Available evidence suggests that many depressions have a biochemical basis in the form of a relative deficiency of neurotransmitters such as norepinephrine and serotonin. Norepinephrine deficiency may be associated with relatively low urinary 3-methoxy-4-hydroxyphenyl glycol (MHPG) levels, while serotonin deficiencies may be associated with low spinal fluid levels of 5-hydroxyindolacetic acid.

While the precise mechanism of action of the tricyclic antidepressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the reuptake of these substances from the synapse in the central nervous system.

Evidence indicates that the secondary amine tricyclic antidepressants, including Norpramin, may have greater activity in blocking the re-uptake of norepinephrine. Tertiary amine tricyclic antidepressants, such as amitriptyline, may have greater effect on serotonin re-uptake.

Norpramin (desipramine hydrochloride) is not a monoamine oxidase (MAO) inhibitor and does not act primarily as a central nervous system stimulant. It has been found in some studies to have a more rapid onset of action than imipramine. Earliest therapeutic effects may occasionally be seen in 2 to 5 days, but full treatment benefit usually requires 2 to 3 weeks to obtain.

INDICATIONS: Norpramin (desipramine hydrochloride) is indicated for relief of symptoms in various depressive syndromes, especially endogenous depression.

CONTRAINDICATIONS: Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS: 1. Extreme caution should be used when this drug is given in the following situations: a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction. b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug. c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias. d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold. **2.** This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds. **3.** USE IN PREGNANCY: Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive. **4.** USE IN CHILDREN: Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. **5.** The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. **6.** In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

PRECAUTIONS: 1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible. This drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly. **2.** If serious adverse effects occur, dosage should be reduced or treatment should be altered. **3.** Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates. **4.** The drug may cause exacerbation of psychosis in schizophrenic patients. **5.** Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs. **6.** Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated. **7.** Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered. **8.** If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin. **9.** This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride. **10.** Both elevation and lowering of blood sugar levels have been reported. **11.** Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutropenia or depression. **12.** Norpramin 25, 50, 75, and 100 mg tablets contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS: Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke.

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depression including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, testicular swelling; elevation or depression of blood sugar levels.

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSAGE AND ADMINISTRATION: Not recommended for use in children. Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients compared to hospitalized patients, who are closely supervised. Dosage should be initiated at a low level and increased according to clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a period of time and should be at the lowest dose that will maintain remission.

Usual Adult Dose: The usual adult dose is 100 to 200 mg per day. In more severely ill patients, dosage may be further increased gradually to 300 mg/day if necessary. Dosages above 300 mg/day are not recommended.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response.

Treatment of patients requiring as much as 300 mg should generally be initiated in hospitals, where regular visits by the physician, skilled nursing care, and frequent electrocardiograms (ECG's) are available.

The best available evidence of impending toxicity from very high doses of Norpramin is prolongation of the QRS or QT intervals on the ECG. Prolongation of the PR interval is also significant, but less closely correlated with plasma levels. Clinical symptoms of intolerance, especially drowsiness, dizziness, and postural hypotension, should also alert the physician to the need for reduction in dosage. Plasma desipramine measurement would constitute the optimal guide to dosage monitoring.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

Adolescent and Geriatric Dose: The usual adolescent and geriatric dose is 25 to 100 mg daily.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response to a usual maximum of 100 mg daily. In more severely ill patients, dosage may be further increased to 150 mg/day. Doses above 150 mg/day are not recommended in these age groups.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

OVERDOSAGE: See prescribing information for a discussion of symptoms and treatment of overdose.

Product Information as of January, 1985.

MERRELL DOW PHARMACEUTICALS INC.
Subsidiary of The Dow Chemical Company
Cincinnati, Ohio 45215, U.S.A.

Merrell Dow

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Sunday, May 10, 1987
7:30-10:30 pm
Chicago Hilton and Towers
International Ballroom
Chicago, Illinois

Psychosis in the Face of Dementia

Princeton Pharmaceutical Products is pleased to announce a symposium designed to examine the incidence and clinical management of psychoses as associated with various dementias, including Alzheimer's disease. A panel of leading psychiatrists will present their views on the neurobehavioral, neuropsychiatric and neurochemical aspects that may differentiate various dementias. The symptomatology and diagnosis of these syndromes will be reveiwed, and the effectiveness of both neuroleptic and non-neuroleptic treatments in psychotic demented patients will be examined.

Jeffrey L. Cummings, MD UCLA School of Medicine	**Dementia Syndrome: Neurobehavioral and Neuropsychiatric Aspects**
Barry Reisberg, MD New York University School of Medicine	**Behavioral Symptomatology of Alzheimer's Disease**
Murray A. Raskind, MD (Chairperson) University of Washington	**Dementia Patients and Antipsychotic Drugs**
Carl Salzman, MD Harvard Medical School	**Treatment of Agitation in the Demented, Psychotic Elderly Patient**
Peter Davies, PhD Albert Einstein College of Medicine	**Neurochemical Studies of Alzheimer's Disease**

PRINCETON PHARMACEUTICAL PRODUCTS
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LIBRIUM®
chlordiazepoxide HCl/Roche Ⓝ
5-mg, 10-mg, 25-mg capsules
Before prescribing, please consult complete product information, a summary of which follows:
Indications: Management of anxiety disorders; short-term relief of anxiety symptoms, acute alcohol withdrawal symptoms, preoperative apprehension and anxiety. Usually not required for anxiety or tension associated with stress of everyday life. Efficacy beyond four months not established by systematic clinical studies. Periodic reassessment of therapy recommended.
Contraindications: Known hypersensitivity to the drug.
Warnings: Warn patients that mental and/or physical abilities required for tasks such as driving or operating machinery may be impaired, as may be mental alertness in children, and that concomitant use with alcohol or CNS depressants may have an additive effect. Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms (including convulsions) reported after abrupt cessation of extended use of excessive doses are similar to those seen with barbiturates. Milder symptoms reported infrequently when continuous therapy is abruptly ended. Avoid abrupt discontinuation; gradually taper dosage.
***Usage in Pregnancy*: Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically. Due to isolated reports of exacerbation, use with caution in patients with porphyria.
Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.
Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral—Adults:* Mild and moderate anxiety disorders and symptoms, 5 or 10 mg *t.i.d.* or *q.i.d.*; severe states, 20 or 25 mg *t.i.d.* or *q.i.d. Geriatric patients:* 5 mg *b.i.d.* to *q.i.d.* (See Precautions.)
Supplied: Librium® (chlordiazepoxide HCl/Roche) *Capsules*, 5 mg, 10 mg and 25 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10. Libritabs® (chlordiazepoxide/Roche) *Tablets*, 5 mg and 10 mg—bottles of 100 and 500; 25 mg—bottles of 100. With respect to clinical activity, capsules and tablets are indistinguishable.

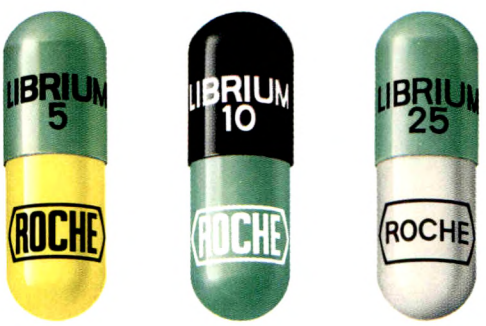
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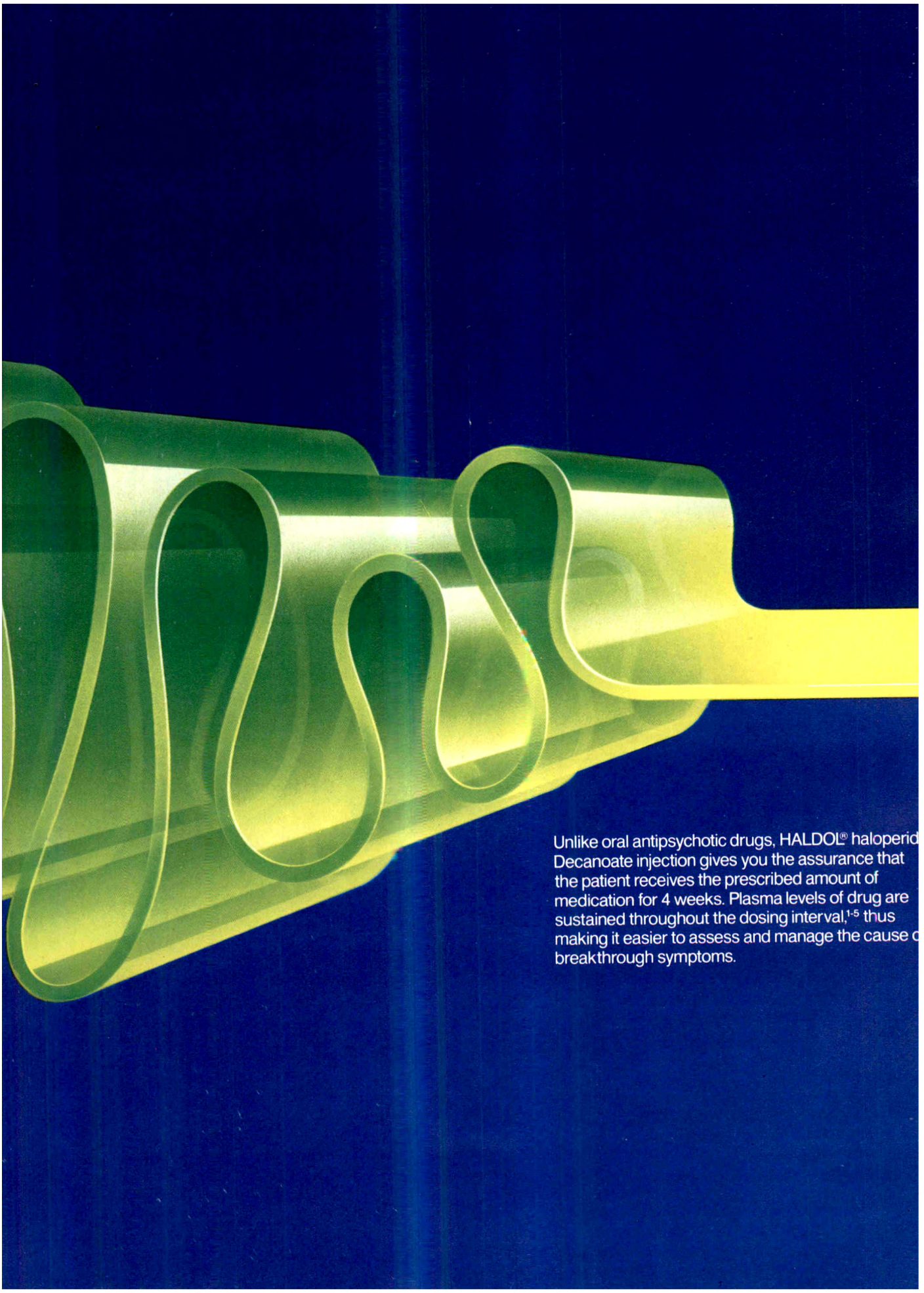


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Please see adjacent page for summary of product information



Unlike oral antipsychotic drugs, HALDOL® haloperid
Decanoate injection gives you the assurance that
the patient receives the prescribed amount of
medication for 4 weeks. Plasma levels of drug are
sustained throughout the dosing interval,[1-5] thus
making it easier to assess and manage the cause o
breakthrough symptoms.

Sustained drug levels with a single monthly dose

HALDOL® DECANOATE
(HALOPERIDOL) INJECTION

the therapeutic constant in schizophrenia

Pharmacokinetic profile facilitates monthly dosing

Smooth, steady drug delivery has been shown to achieve efficacy equal to oral HALDOL, but at lower monthly doses.[1] The plasma concentrations of haloperidol gradually rise, reaching a peak at about 6 days after the injection, and falling thereafter, with an apparent half-life of about 3 weeks.[6]

The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects. During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL. It is recommended that patients being considered for HALDOL Decanoate therapy have, at some time, been treated with, and have tolerated well, short-acting HALDOL in order to exclude the possibility of unexpected adverse sensitivity to haloperidol. HALDOL Decanoate is administered only by deep intramuscular injection.

Offers sustained protection against schizophrenic relapse

Dependable delivery with HALDOL Decanoate helps provide protection for your patient to withstand the demands of daily life.

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Please see brief summary of prescribing information on next page.

McNEIL PHARMACEUTICAL
McNEIL AB, INC., Spring House, PA 19477

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HALDOL DECANOATE
(HALOPERIDOL) INJECTION



Sustained protection for the schizophrenic patient with a single monthly dose

The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5 and 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis: the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia and tardive dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Other CNS Effects:* Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and cataatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic Malignant Syndrome: As with other antipsychotic drugs, a symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported. Cardinal features of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. NMS is potentially fatal, requires intensive symptomatic treatment and immediate discontinuation of antipsychotic treatment. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported. *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.
For information on symptoms and treatment of overdosage, see full prescribing information.

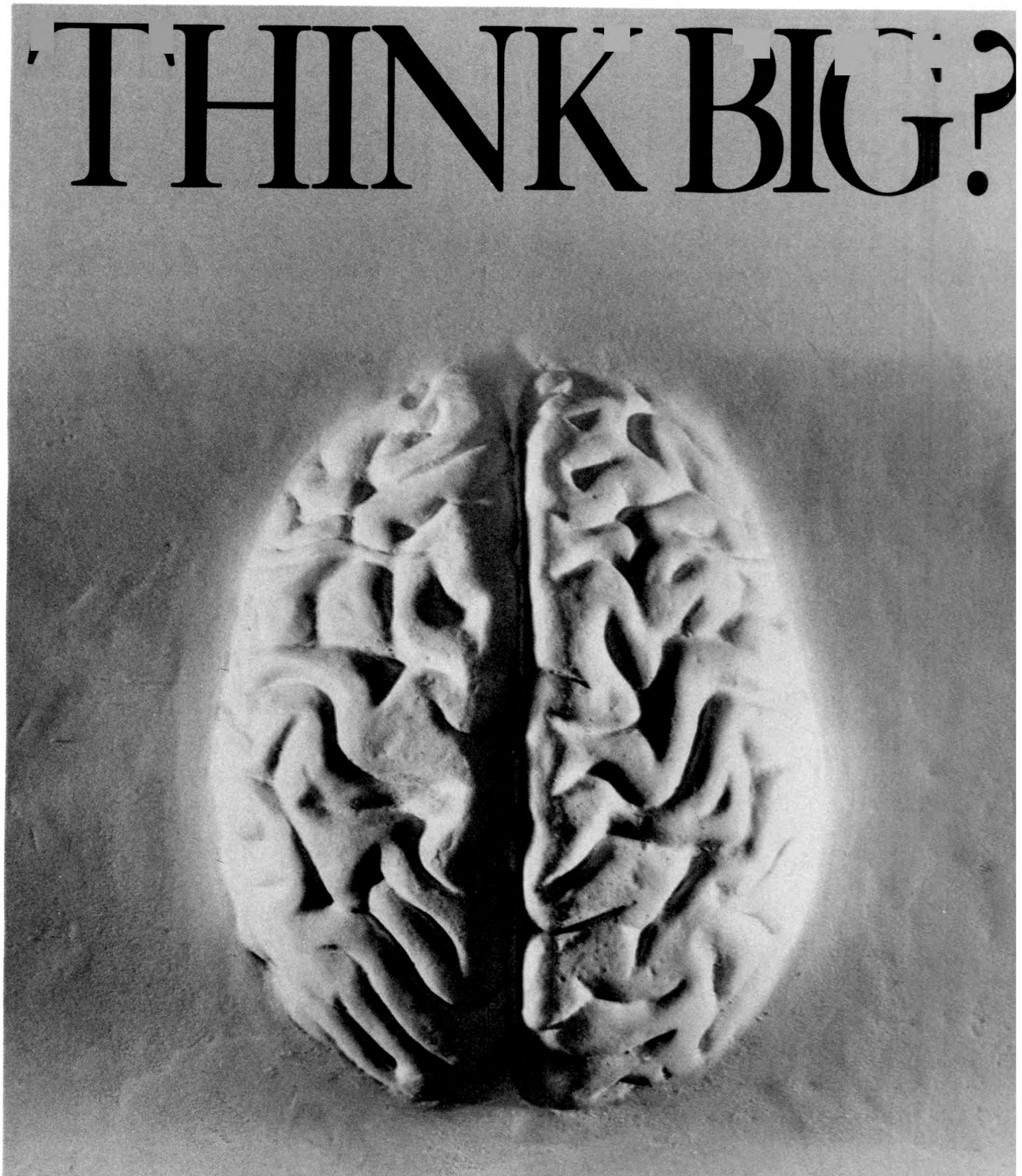
The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

11/10/86

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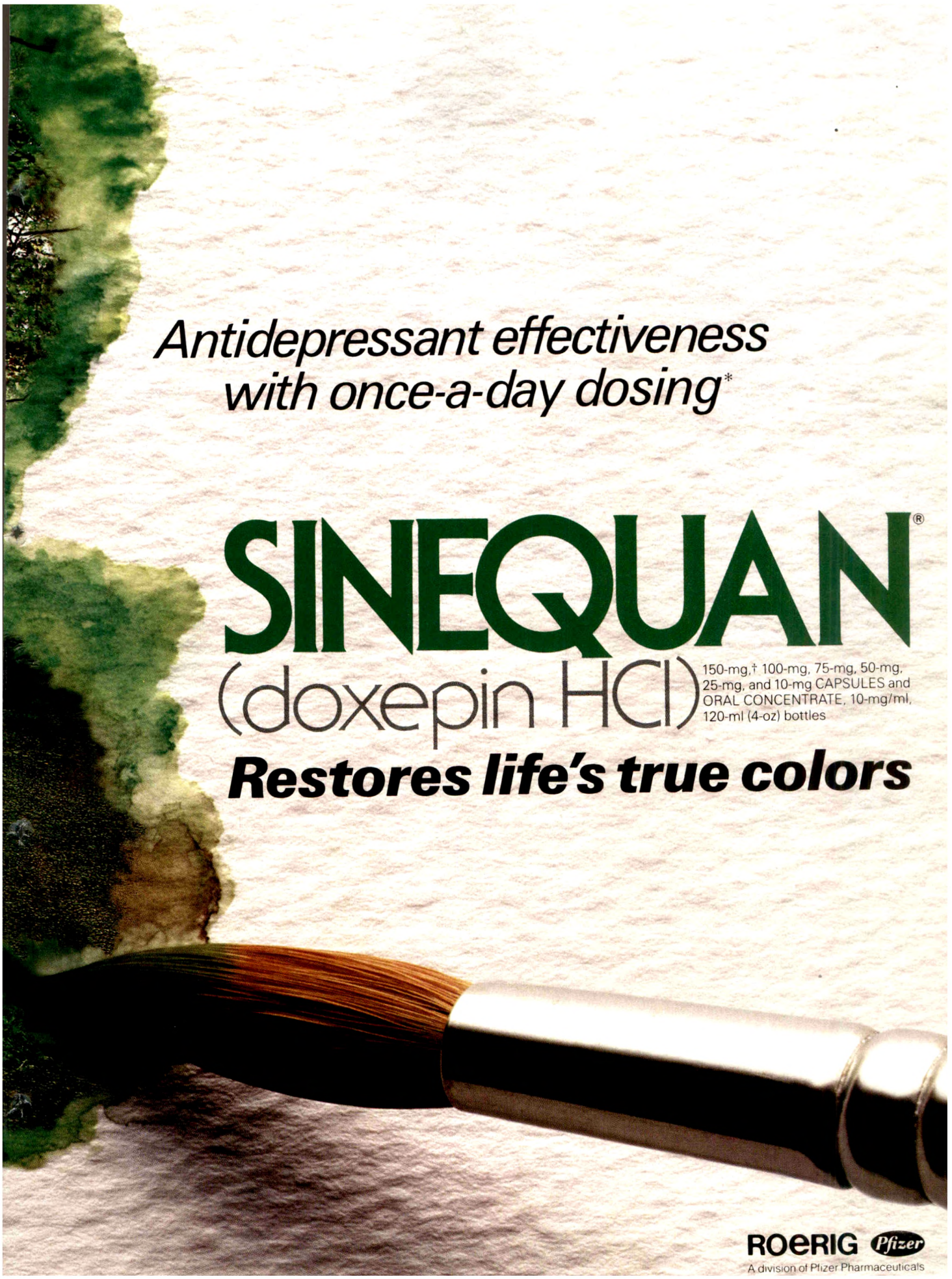


*The total daily dosage of Sinequan may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg. This dose may be given at bedtime.

†**The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

For a brief summary of SINEQUAN prescribing information including adverse reactions, please see the following page of this advertisement.

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Antidepressant effectiveness
with once-a-day dosing*
SINEQUAN®
(doxepin HCl)
150-mg,† 100-mg, 75-mg, 50-mg,
25-mg, and 10-mg CAPSULES and
ORAL CONCENTRATE, 10-mg/ml,
120-ml (4-oz) bottles
Restores life's true colors
ROERIG
Pfizer
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SINEQUAN® (doxepin HCl)

BRIEF SUMMARY
SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate
Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.
A. Signs and Symptoms
1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment
1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

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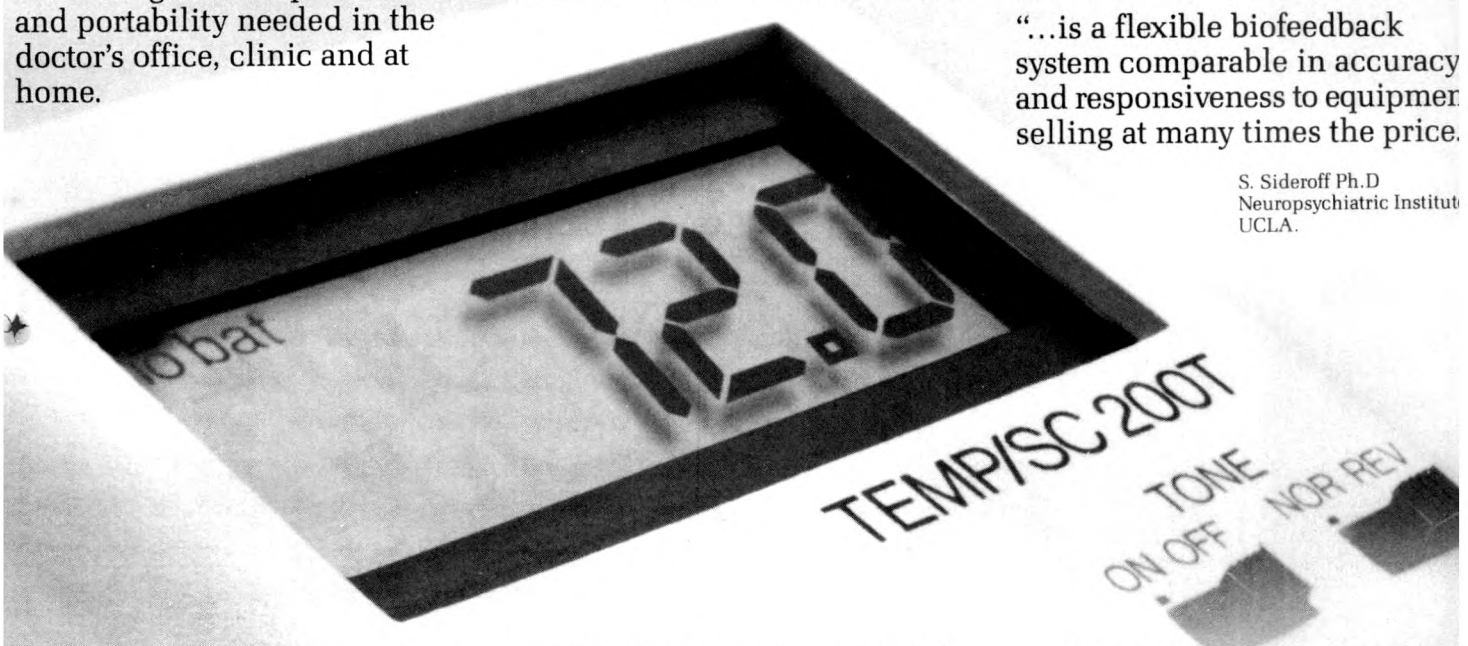
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☐ GSR/TEMP 2™ @ $129.00 plus $8.00

TOTAL _____

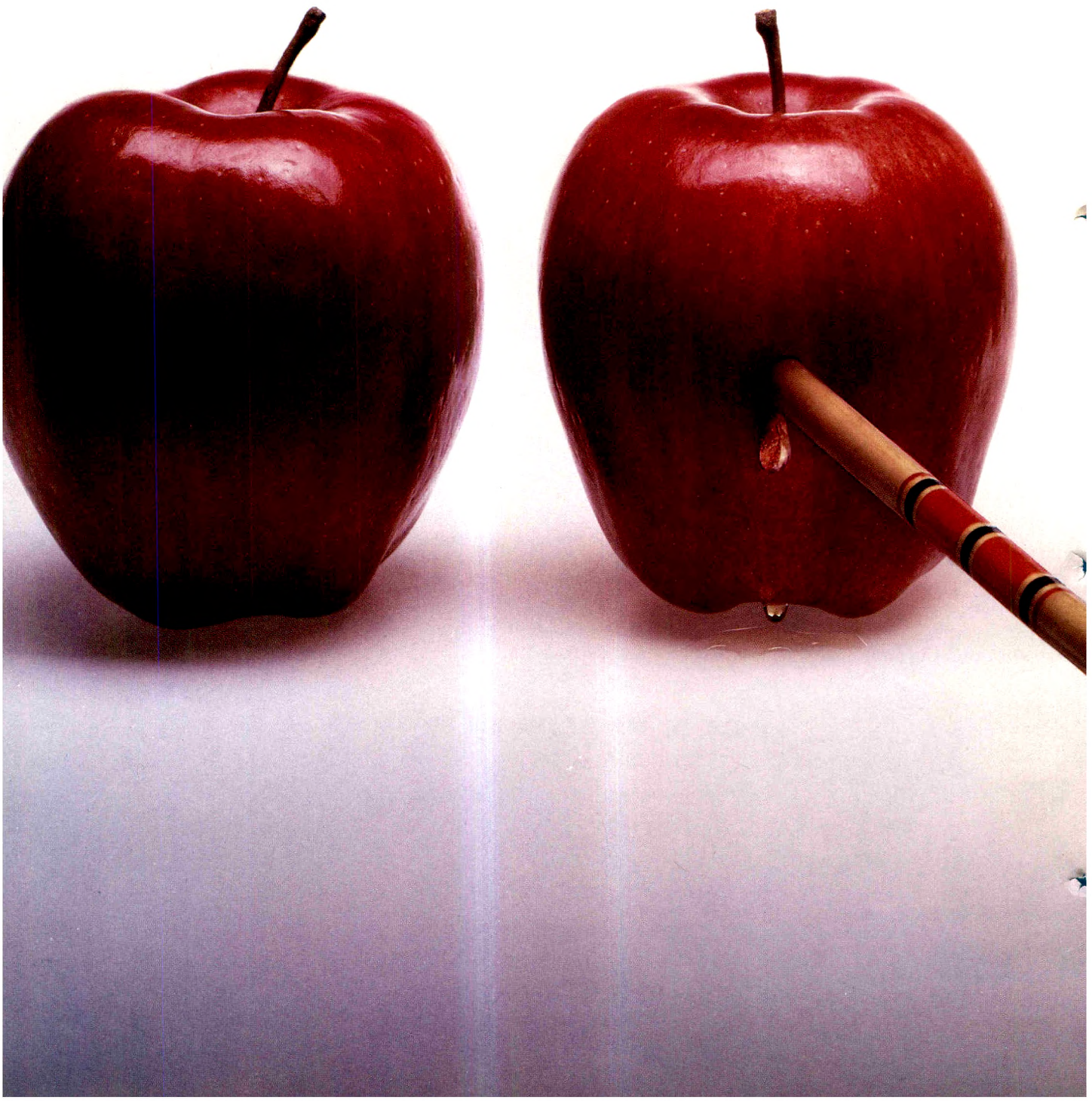
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Between the side-effect extremes





On-target control of psychosis

"The least potent antipsychotics (chlorpromazine and thioridazine) tend to be the most sedating and to have the most anticholinergic effects."[1]

LOXITANE provides moderate sedation and causes fewer anticholinergic effects than lower potency neuroleptics[2]—less than 1% incidence of hypotension or syncope in clinical trials.[3]

"The relatively more potent agents, especially haloperidol and fluphenazine, cause the highest incidence of side effects in the extrapyramidal system."[1]

LOXITANE causes fewer extrapyramidal effects than more potent neuroleptics.[2]

Aim for the Center

LOXITANE

loxapine succinate/hydrochloride

Please see the next page for a brief summary of prescribing information.

LOXITANE®

loxapine succinate/hydrochloride



Available in three forms for easier dosing

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loxapine hydrochloride Intramuscular
50 mg base/ml—Each ml contains the equivalent of 50 mg loxapine base as the HCl

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loxapine hydrochloride Oral Concentrate
25 mg base/ml in bottles of 4 fl oz

LOXITANE loxapine succinate Capsules
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All dosage forms with milligram-for-milligram equivalency

LOXITANE® loxapine succinate Capsules
LOXITANE® C loxapine hydrochloride Oral Concentrate
LOXITANE® IM loxapine hydrochloride

INDICATIONS: LOXITANE is indicated for the management of the manifestations of psychotic disorders. The antipsychotic efficacy of LOXITANE was established in clinical studies which enrolled newly hospitalized and chronically hospitalized acutely ill schizophrenic patients as subjects.
CONTRAINDICATIONS: Comatose or severe drug-induced depressed states (alcohol, barbiturates, narcotics, etc); hypersensitivity to the dibenzoxazepines.
WARNINGS: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increases. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low dosages.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dosage and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

Mental and or physical abilities may be impaired, especially during early therapy; warn ambulatory patients about activities requiring alertness, about concomitant use of alcohol and other CNS depressants. Not recommended for management of behavioral complications in mentally retarded patients.
PRECAUTIONS: Use with extreme caution in patients with a history of convulsive disorders; seizures have been reported in epileptic patients receiving antipsychotic dosage levels and in epileptic patients with maintenance of anticonvulsant therapy. Use with caution in patients with cardiovascular disease or in those with glaucoma or a tendency to urinary retention, particularly when on concomitant anticholinergic medication. Loxapine has an antiemetic effect in animals which might occur in man, masking signs of overdosage of toxic drugs and obscuring intestinal obstruction or brain tumor. Since possible ocular toxicity cannot be excluded, observe carefully for pigmentary retinopathy and lenticular pigmentation. Slightly higher incidence of extrapyramidal effects possible following IM administration than normally anticipated with oral formulations.

Neuroleptic drugs elevate prolactin levels; elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Safe use during pregnancy or lactation or by women of child-bearing potential has not been established; weigh potential benefits against possible risks to mother and child. No embryotoxicity or teratogenicity was observed in studies in rats, rabbits, or dogs, although, with the exception of one rabbit study, the highest dosage was only two times the maximum recommended human dosage, and in some studies it was below this dosage. Perinatal studies have shown renal papillary abnormalities in offspring of rats treated from midpregnancy with doses of 0.6 to 1.8 mg/kg doses which approximate the usual human dose but which are considerably below the maximum recommended human dose. It is known that this drug and its metabolites have been transported into the milk of lactating dogs. LOXITANE® *loxapine* administration to nursing women should be avoided, if clinically possible. Not recommended for use in children under 16.
ADVERSE REACTIONS: *CNS Effects:* Other than extrapyramidal, have been seen infrequently. Drowsiness, dizziness, faintness, staggering gait, shuffling gait, muscle twitching, weakness, insomnia, agitation, tension, seizures, akinesia, slurred speech, numbness, and confusional states have been reported. Neuroleptic malignant syndrome (NMS) has been reported. *Extrapyramidal Reactions:* Neuromuscular (extrapyramidal) frequently, often during the first few days of treatment. Reactions involved parkinsonian-like symptoms such as tremor, rigidity, excessive salivation, and masked facies. Akathisia (motor restlessness) also has been reported relatively frequently. Dystonic and dyskinetic reactions have occurred less frequently, but may be more severe. Dystonias include spasms of muscles of the neck and face, tongue protrusion, and oculogyric movement. Dyskinetic reactions have been described in the form of choreoathetoid movements. These reactions sometimes require reduction or temporary withdrawal of loxapine dosage in addition to appropriate counteractive drugs.

Persistent Tardive Dyskinesia: As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. Risk appears to be especially greater in elderly female patients on high-dosage therapy. Symptoms are persistent and in some patients appear to be irreversible. Syndrome is characterized by rhythmical involuntary movement of the tongue, face, mouth, or jaw (eg, protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities. *Cardiovascular Effects:* Tachycardia, hypotension, hypertension, orthostatic hypotension, lightheadedness, and syncope. A few cases of ECG changes have been reported. *Hematologic:* Rarely, agranulocytosis, thrombocytopenia, leukopenia. *Skin:* Dermatitis, edema (puffiness of face), pruritus, rash, alopecia, and seborrhea. *Anticholinergic Effects:* Dry mouth, nasal congestion, constipation, blurred vision, urinary retention, and paralytic ileus. *Gastrointestinal:* Nausea, vomiting, and hepatocellular injury (ie, SGOT/SGPT elevation). Rarely, jaundice and/or hepatitis. *Other:* Weight gain, weight loss, dyspnea, ptosis, hyperpyrexia, flushed facies, headache, paresthesia, and polydipsia. Rarely, galactorrhea, amenorrhea, gynecomastia, and menstrual irregularity of uncertain etiology.
OVERDOSAGE: Signs and symptoms are those expected from the pharmacological actions and amount ingested. Can range from mild depression of CNS and cardiovascular symptoms to profound hypotension, respiratory depression and unconsciousness. Extrapyramidal symptoms and convulsive seizures have occurred as well as renal failure. Treatment is essentially symptomatic and supportive. Early gastric lavage with dialysis might be expected to be beneficial. *Avoid* use of centrally acting emetics, analeptics, and epinephrine.

Rev. 1.86

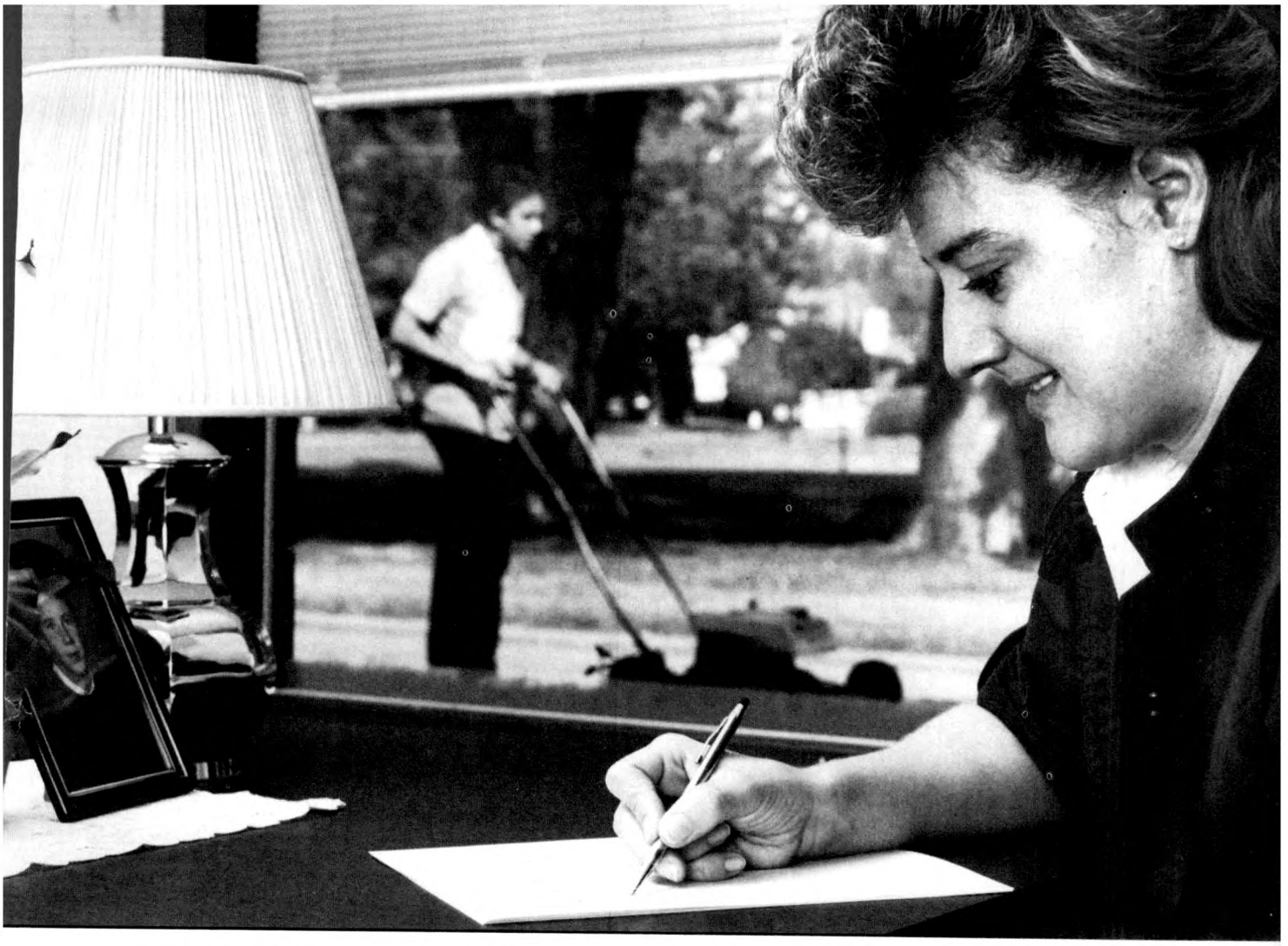
References:

1. Thompson TL II, Moran MG, Nies AS: Psychotropic drug use in the elderly. *New Engl J Med* 1983; 308:194-198.
2. Rhoades HM, Overall JE: Side effect potentials of different antipsychotic and antidepressant drugs. *Psychopharmacol Bull* 1984; 20:83-88.
3. Data on file, Lederle Laboratories, Pearl River, N.Y.

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MELLARIL therapy is contraindicated in patients with hypertensive or hypotensive heart disease of extreme degree.



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MELLARIL-S® (thioridazine) SUSPENSION: 25 mg/5 ml (each 5 ml contains thioridazine, USP, equivalent to 25 mg thioridazine HCl, USP) and **100 mg/5 ml** (each 5 ml contains thioridazine, USP, equivalent to 100 mg thioridazine HCl, USP)

FOR ORAL ADMINISTRATION

Caution: Federal law prohibits dispensing without prescription.

Before prescribing or administering, see Sandoz literature for full product information. The following is a brief summary.

Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree.

Warnings: The risk of developing potentially irreversible *tardive dyskinesia* is believed to increase as duration of treatment and total cumulative dose increase, although it is impossible to predict who will develop the syndrome. It can also develop, although much less commonly, after brief treatment with low doses. Incidence appears to be highest among the elderly, especially elderly women. Generally chronic treatment should be reserved for chronically ill patients whose disease is most likely to respond to neuroleptic drugs and for whom other effective, less harmful treatment is not available or appropriate. There is no known treatment for tardive dyskinesia although the syndrome may partially or completely remit upon withdrawal of neuroleptic treatment. If signs and symptoms of tardive dyskinesia appear, drug discontinuation should be considered. Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides; carefully consider benefit versus risk in less severe disorders. During pregnancy, administer only when the potential benefits exceed the possible risks to mother and fetus.

Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy, observed primarily in patients receiving larger than recommended doses, is characterized by diminution of visual acuity, brownish coloring of vision, and impairment of night vision; the possibility of its occurrence may be reduced by remaining within recommended dosage limits. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving), and increase dosage gradually. Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension since phenothiazines may induce a reversed epinephrine effect on occasion.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. Daily doses in excess of 300 mg should be used only in severe neuropsychiatric conditions.

Information for Patients: It is suggested that all patients who are candidates for chronic treatment be advised of the risk of tardive dyskinesia.

Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; rarely, nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—ECG changes (see *Cardiovascular Effects* below). *Other*—Rare cases described as parotid swelling.

It should be noted that efficacy, indications and untoward effects have varied with the different phenothiazines. It has been reported that old age lowers the tolerance for phenothiazines; the most common neurological side effects are parkinsonism and akathisia, and the risk of agranulocytosis and leukopenia increases. The following reactions have occurred with phenothiazines and should be considered whenever one of these drugs is used:

Autonomic Reactions—Miosis, obstipation, anorexia, paralytic ileus. *Cutaneous Reactions*—Erythema, exfoliative dermatitis, contact dermatitis. *Blood Dyscrasias*—Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia. *Allergic Reactions*—Fever, laryngeal edema, angioneurotic edema, asthma. *Hepatotoxicity*—Jaundice, biliary stasis. *Cardiovascular Effects*—Changes in the terminal portion of electrocardiogram including prolongation of Q-T interval, lowering and inversion of T-wave, and appearance of a wave tentatively identified as a bifid T or a U wave have been observed with phenothiazines, including Mellaril (thioridazine); these appear to be reversible and due to altered repolarization, not myocardial damage. While there is no evidence of a causal relationship between these changes and significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients showing characteristic electrocardiographic changes while taking the drug. While proposed, periodic electrocardiograms are not regarded as predictive. Hypotension, rarely resulting in cardiac arrest. *Extrapyramidal Symptoms*—Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonus, oculogyric crises, tremor, muscular rigidity, and akinesia. *Tardive Dyskinesia*—Characterized by involuntary choreoathetoid movements variously involving the tongue, face, mouth, lips or jaw (e.g., protrusion of the tongue, puffing of the cheeks, puckering of the mouth, chewing movements), trunk and extremities—may be recognized during treatment upon dosage reduction or withdrawal of treatment. Movements may decrease or disappear if further treatment is withheld, although this reversibility is more likely after short-term rather than long-term treatment. Since neuroleptics may mask the signs of tardive dyskinesia, reducing dosage periodically increases the likelihood of detecting the syndrome at the earliest possible time. *Endocrine Disturbances*—Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema, false positive pregnancy tests. *Urinary Disturbances*—Retention, incontinence. *Others*—Hyperpyrexia; behavioral effects suggestive of a paradoxical reaction, including excitement, bizarre dreams, aggravation of psychoses, and toxic confusional states; following long-term treatment, a peculiar skin-eye syndrome marked by progressive pigmentation of skin or conjunctiva and/or accompanied by discoloration of exposed sclera and cornea; stellate or irregular opacities of anterior lens and cornea; systemic lupus erythematosus-like syndrome.

Dosage: Dosage must be individualized according to the degree of mental and emotional disturbance, and the smallest effective dosage should be determined for each patient. [MEL-Z37—5/1/85]

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MEL-1185-29

THE AMERICAN JOURNAL OF PSYCHIATRY

Intensive Psychodynamic Therapy With Borderline Patients: An Overview

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The author reviews major controversies in the literature regarding techniques of intensive psychodynamic therapy with borderline patients. These include debates about 1) the importance of content versus process in the therapist's early interventions, 2) the origins of transference, 3) the primacy of positive versus negative transference in therapeutic work, 4) the usefulness of early interpretation of negative transference, and 5) the therapist's role in providing "corrective" experiences. He suggests that different conceptions of borderline psychopathology, different patient populations studied, variations in therapists' personality styles, and emphasis on different phases of treatment may account for the diversity of treatment techniques advocated in the literature.

(Am J Psychiatry 1987; 144:267–274)

The treatment of borderline patients has long been characterized as an arduous task. Indeed, early clinical descriptions of the borderline syndrome (1, 2) arose out of the treatment difficulties these patients posed. Intense hostile-dependent transferences, severe regressive reactions, self-destructive and sometimes violent behaviors, and transient lapses into psychosis were all characteristics that caused the borderline patient to be treated with caution.

It is little wonder that clinicians began to write about strictly limiting treatment of borderline patients to supportive psychotherapeutic interventions (3, 4). Zetzel (5) was a prominent advocate of a highly structured, supportive approach in which patients are seen infrequently (often no more than once a week) and the therapist sets limits on patients' unrealistic demands for time and attention. Zetzel argued that these limitations allowed the therapy to proceed without the development of unworkable regressive transference reactions. Even so, she was pessimistic about the borderline patient's capacity to internalize a sufficiently stable ego identification to become genuinely autonomous. She believed that borderline patients might need access throughout their lives to a therapist or some other person who could perform for them those ego functions which they would never be capable of performing on their own.

Subsequent writers on the subject of the psychodynamic treatment of borderline patients have shared Zetzel's sense of the difficulty of this work. However, in the last two decades there has been a burgeoning of literature on the usefulness of intensive exploratory psychotherapy with borderline patients—treatment aimed not simply at crisis management or improved social role performance but at the resolution of the pathological constellation that is thought to lie at the heart of this disorder.

In this paper, I review the major controversies in the literature regarding techniques of intensive psychotherapy with borderline patients. My aim is not to give "equal time" to the many people who have written on this subject but, rather, to summarize and compare the ideas of a few authors who have most clearly articulated distinct viewpoints on controversial issues and on whom debates about therapeutic technique have centered (an expanded version of this discussion can be found in Waldinger and Gunderson [6]).

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The author thanks Arlene Frank, Ph.D., John Gunderson, M.D., and Gerald Adler, M.D., for their comments on this manuscript.

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INTENSIVE TREATMENT OF THE BORDERLINE PATIENT

Definitions of intensive treatment vary. Some authors, such as Masterson (7), Buie and Adler (8), and Kernberg (9), write about dynamically oriented face-to-face psychotherapy conducted two or three times per week. Others, including Boyer (10). Giovacchini (11), Volkan (12) and Chessick (13), conceive of intensive treatment as classical psychoanalysis conducted on the couch five times per week. Moreover, labels for intensive treatment differ. Intensive psychodynamic therapy has been labeled "expressive" by Kernberg (14), "reconstructive" by Masterson (7), and "psychoanalytically informed" by Chessick (15). However, virtually all of these clinicians agree on certain basic tenets of safe and effective intensive treatment of the borderline patient.

1. *Stability of the framework of treatment.* All of these writers agree on the importance of establishing regular appointment times, beginning and ending sessions on time, and making clear from the outset the therapist's expectations about keeping appointments, paying fees, and other framework issues. Any deviations from the framework by the patient or by the therapist (e.g., missed appointments) should be actively addressed and the patient's feelings about such deviations explored in the therapy hours.

2. *Increased activity of the therapist.* Compared to the treatment of a neurotic patient, work with borderline patients requires that the therapist actually say more during the treatment hours. The value of these comments to the patient lies not only in their content but also in the fact that they serve to emphasize the therapist's presence to anchor the patient in reality, and to minimize the severity of transference distortions, which borderline patients are prone to develop in unstructured situations.

3. *Tolerance of the patient's hostility.* The therapist must be able to withstand the borderline patient's verbal assaults without either retaliating or withdrawing, so that the patient's hostility toward the therapist is not buried but examined and understood as part of a more general pattern of relating to important others.

4. *Making self-destructive behaviors ungratifying.* Borderline patients are highly invested in remaining unaware of the self-destructive nature of actions that gratify certain wishes and allay anxiety. The therapist must consistently and repeatedly draw the patient's attention to the adverse consequences of behaviors such as drug use, promiscuity, manipulativeness, and inappropriate rageful outbursts—focusing not on the patient's stated motives for such activities but on the results.

5. *Establishing a connection between the patient's actions and feelings in the present.* For borderline patients, action is a primary defense against the awareness of uncomfortable affects. Since such awareness is considered essential to the development of autonomy and self-control, the patient must be helped to see that he or she communicates through action and that this serves a defensive function.

6. *Blocking acting-out behaviors.* In contrast to the neurotic patient, who may at times act out transference feelings and in doing so gain new insight into unconscious motives and fantasies, the borderline patient uses acting out as a major resistance to the awareness of transference and, thus, to the progress of treatment. The therapist must set limits on behaviors that threaten the safety of the patient, the therapist, or the therapy.

7. *Focusing early clarifications and interpretations on the here and now.* Genetic interpretations or attempts at genetic reconstructions early in treatment are likely to be counterproductive, as they divert attention from the immediate and often dangerous pathological behaviors that disrupt the patient's life.

8. *Careful attention to countertransference feelings.* Persistent monitoring of countertransference reactions is necessary to minimize the very real danger of acting out on the part of the therapist. Most authors agree that the therapist's own experience as a patient in dynamic psychotherapy facilitates this process by helping the therapist to better understand and use his or her emotional reactions in the treatment. (A detailed discussion of the management and therapeutic uses of the therapist's emotional reactions to the borderline patient is beyond the scope of this paper. The reader is referred to the work of Boyer [16] and Searles [17] for more extensive discussion of this important subject.)

DIFFERENCES IN TECHNIQUE

Despite the points of general agreement that I have noted, there are major differences in technique among those who write about intensive treatment of borderline patients, and it is these differences which will be highlighted here. Areas of major disagreement are to be found in the literature on five broad issues: 1) the importance of content versus process in the therapist's early interventions, 2) the origins of the patient's transference to the therapist, 3) the primacy of positive versus negative transference in therapeutic work, 4) the usefulness of early interpretation of negative transference, and 5) the therapist's role in providing new "corrective" experiences for the borderline patient in therapy. These issues are summarized in table 1.

Interpretation Versus Creation of a Holding Environment

Borderline patients are notoriously difficult to engage in psychotherapy, and they commonly flee treatment shortly after it has begun (18). Clinicians disagree about whether transference interpretations are useful in maintaining a stable therapeutic framework early in treatment or whether the creation of a holding environment is what is essential in weathering the storms of the first phases of therapy.

TABLE 1. Differences Among Writers Concerning the Theory and Technique of Intensive Therapy With Borderline Patients

Author	Etiology of Syndrome	Nature of Pathology	Early Interpretation of Transference	Essential Early in Treatment	Origin of Transference	Therapist's Role in Patient's Experiential Learning
Buie and Adler	Environment	Deficit	No	Provide holding environment	Real disturbance in primary relationships	Active structuring: validation of patient's positive qualities
Chessick	Environment	Deficit	No	Provide holding environment	Real disturbance in primary relationships	Inherent in framework: therapist is object for internalizations
Giovacchini	Environment plus (?) constitution	Deficit	No	Provide holding environment	Real disturbance in primary relationships	Inherent in framework: soothing qualities of therapist and setting
Gunderson	Constitution plus environment	Conflict/ deficit	No	Explore negative transference	Real disturbance plus patient's distortions of primary relationships	Active structuring: validation of patient's new feelings and perceptions
Kernberg	Constitution plus environment	Conflict	Yes	Interpret primitive defenses used *in* sessions	Real disturbance plus patient's distortions of primary relationships	Inherent in framework: therapist does not retaliate or withdraw
Masterson	Environment	Conflict	No	Interpret acting out as related to affect	Real disturbance in primary relationships	Active structuring: communicative matching

Interpretation: the usefulness of content. Kernberg (9) believes that borderline patients are capable of responding to the actual meaning of interpretive comments by the therapist early in treatment, but only if interpretations are properly framed. He writes that the use of primitive defenses (e.g., splitting, denial, projection, and primitive idealization) leaves the borderline patient incapable of participating in relationships without grossly distorting them. Like all other aspects of a relationship, the therapist's comments are bound to be distorted by the patient. Kernberg believes that borderline patients are able to "hear" the actual meaning of interpretive comments only when transference distortions of such comments (e.g., "the therapist loves me" or "the therapist is my sadistic father") have been brought to light. For example, a patient who is invested in projecting his sadism onto others may hear every interpretation made by the therapist as an attack and therefore be unable to make use of its content. Kernberg argues that by clarifying such misperceptions immediately in the therapy hour, primitive defenses can be replaced by higher level ones, resulting in a stronger ego, less distortion of interpersonal relationships, and the capacity to use the therapist's interventions. Boyer (10) employs an interpretive strategy much like Kernberg's, in that transference interpretations are coupled with careful attention to the patient's experience of the interpretive process itself.

Masterson (19), too, assumes that borderline patients can make use of interpretive content. He sees borderline individuals as using primitive defenses and maladaptive behaviors to ward off abandonment depression. He emphasizes that the therapist's first task is to control acting out by repeatedly clarifying the self-destructive nature of these maneuvers in order to make them ego dystonic. Once this is accomplished, Masterson believes, the content of interpretation can be heard without gross distortions. Unlike Kernberg, Masterson does not emphasize the borderline patient's tendency to distort the therapist's comments in the therapy hours.

Gunderson (20) believes that the borderline patient's ability to understand and use the content of interpretations fluctuates widely, depending on the patient's level of anxiety and sense of relatedness to the therapist. He argues that at any given moment, the therapist must assess whether the patient feels supported by and involved in the therapy, and is thus able to use interpretations, or whether this ability has been temporarily lost as a result of some current stress (e.g., an impending separation).

The holding environment: the importance of process. On the opposite side of this debate are writers like Buie and Adler (8), who argue that the borderline patient's experience of being empathically held in therapy is the essential ingredient at the beginning of successful treatment. Since Buie and Adler view the core of borderline pathology as a failure in the development of holding and soothing introjects, their goal is not to undo what is already there and malformed (as Kernberg and Masterson propose) but to create what never existed: "to promote intrapsychic structural development to redress this developmental failure" (8, p. 54). This requires the patient to use the therapist as a holding self-object, that is, as someone who can perform the holding and soothing functions for the patient which the patient cannot perform on his or her own. The concept of providing a holding environment for the patient is consistent with classical psychoanalytic technique, insofar as the interpretive process and

the stability of the psychoanalytic framework are seen as "holding" (21, 22). But Buie and Adler extend this concept beyond classical technique, so that the therapist functions *in reality* as a stable, holding self-object for the borderline patient. This may involve offering considerable support, including hospitalization, extra appointments, telephone calls between therapy hours, giving vacation addresses, and even sending the patient postcards during the therapist's absences (8, 23). It is not interpretive content per se that is healing, but the fact that the therapist is a stable, consistent, caring, nonpunitive person who survives the patient's rage and destructive impulses and continues to serve the holding function. The mode by which the patient learns is primarily experiential, and interpretations highlight the patient's ego defects more than conflicts. Interpretation and confrontation are used early in treatment only insofar as they help create this stable environment.

The view that experiential factors are more important than the content of interpretations for borderline patients in the early phases of treatment is shared by Volkan (12) and Chessick (24), who write about the importance of alliance building as well as providing a holding environment early in treatment. Gunderson (20), too, stresses the importance of the holding environment—especially in the beginning phases of treatment—as necessary to address the borderline patient's state of objectlessness, so that interpretation can then be useful to the patient.

The Origins of Transference

Writers disagree about the origin of the borderline patient's notoriously intense primitive transferences. Some authors see transference as originating entirely in the patient's real relationships with primary caretakers. Others argue that transference arises to a large extent from the patient's defensive distortions of these early relationships.

Kernberg (9) takes the latter position. He writes that the borderline patient's transference to the therapist originates largely in the fantasy distortions which accompany early object relationships. The small child mobilizes primitive defenses to extricate himself or herself from threatening interpersonal relationships and thus creates "monsters," where in reality only imperfect parents exist.

Whereas Kernberg emphasizes the fantasy basis of the borderline patient's transference, Masterson emphasizes the reality basis, stating that the mother of every borderline patient is herself a borderline (7, 19, 25). While he claims not to blame the mother for whatever goes wrong in the borderline patient's development, in his many case examples he makes few distinctions between real and fantasied aspects of early object relationships. In similar fashion, Chessick (15) traces the roots of borderline psychopathology to interactions with the mother but acknowledges that social change and a breakdown in stable social networks interfere with the mother's capacity to provide a calm and secure environment. Buie and Adler (8), like Masterson, see the patient's mistrust of and rage at the therapist as primarily reactive to "not-good-enough mothering"; i.e., they see negative transference as based on real past experience.

These differences in emphasis have important implications for how these writers see the development of transference and how they work with it in psychotherapy. Masterson treats transference as the reflection of the patient's real early experiences, and he works with it as such. Interpretations are made with the aim of helping the patient to differentiate between the current reality of the therapy relationship and distortions of it based on what happened to the patient in the past.

Kernberg, by contrast, sees transference as existing at two levels in the borderline patient: a primitive type that is the product of gross distortions of childhood experiences by primitive defenses and a higher level transference based on real childhood experiences. Kernberg (9) actually sees a shift in the transference from the more primitive to the more realistic as therapy proceeds and the patient's ego functioning becomes more mature and less distorting. Gunderson (20) agrees with Kernberg on this point.

The Primacy of Positive Versus Negative Transference

Those who study the psychotherapy of borderline patients differ in the relative importance they attach to working with positive and negative transference.

Buie and Adler (8) see idealizing transferences as the core of borderline pathology. They view the analysis of negative transference as a preliminary step that clears the way for the emergence of the more fundamental idealizing self-object transference. This unrealistic positive transference is ameliorated by what Kohut (26) termed "optimal disillusionment," a process by which patients gradually notice discrepancies between the idealized holding introject and the actual holding qualities of the therapist. Each disappointment (e.g., the therapist's vacation or absence due to illness), if it is "optimal" and not overwhelming, prompts the patient to develop insight into the unrealistic aspects of his or her positive feelings for the therapist. The therapist is ultimately accepted as he or she is, and the patient's holding introjects are modified accordingly. The therapist's job during this phase is to stay with the patient empathically, to provide clarifications and interpretations of the dynamic and genetic bases for these disappointments, and to avoid any confrontations that would intensify these disappointments (8).

Kernberg (9, 14) does not assign positive transference the central place afforded it in the treatment strategies of Buie and Adler. Rather, he sees negative transference as the primary manifestation of borderline pathology and the working through of negative transference as the primary task of treatment. He most often describes positive transference as defensive ide-

alization used to protect borderline patients from their negative transference and as avoidance of more mature object relations.

One might liken the contrast between these two views to a figure-ground problem in drawing. While Buie and Adler see the patient's positive feelings as the background upon which negative transference is the overlay, Kernberg sees the two in reverse. What results are divergent views of what constitutes the core of treatment: the interpretation of negative transference (Kernberg) or the progressive disillusionment of idealizing transference (Buie and Adler). These divergent views imply different ways of understanding the patient's behavior and material during the therapy hours. For example, Kernberg might be inclined to see the patient's idealization of the therapist as a defense against deeply rooted hostility. Buie and Adler, on the other hand, would be more likely to see the idealization as primary and the patient's hostility as secondary to disappointment.

Early Interpretation of Transference

The debate about whether the borderline patient's hostility is primary or secondary gives rise to divergent treatment recommendations, particularly with respect to the early phases of psychotherapy. Kernberg cautions that unless the therapist interprets the borderline patient's hostility and shows that he or she can tolerate it from the outset of treatment, negative feelings will be forced "underground" and will secretly undermine the therapeutic endeavor.

By contrast, therapists such as Chessick, Giovacchini, and Adler, who see the patient's problem in terms of deficits of holding and soothing introjects, focus on the narcissistic vulnerabilities of the borderline personality and have introduced the technical modification of accepting the patient's idealization and derogation without interpretation for a long time. Adler (27) writes that this idealized self-object transference and the patient's longings for a perfect caregiver are what hold the borderline patient in treatment. According to this view, early interpretation of negative transference is likely to be heard by the patient as criticism, which would disrupt the patient's sense of being empathically held by the therapist and thus destroy the patient's motivation for treatment. Giovacchini (11) notes a similar hazard and advises against early interpretation.

Chessick (15) sees the borderline patient as needing to internalize an idealized image of the therapist in order to develop a more stable self view. While he acknowledges that the borderline patient's idealization of the therapist can serve as a defense against rage, he believes it is best not to confront this idealized image early in treatment, unless the patient's affect is so intense (e.g., so erotized) that the work of therapy becomes disrupted by it (28).

Grotstein (29) writes that deeply regressed borderline patients may be incapable of using the content of transference interpretations, because they need the therapist to function as a "container" for their fragmented psyches and cannot hear interpretations about their projections until they have sufficient ego strength to tolerate the warded-off aspects of themselves. Searles cautions the therapist against early interpretation of transference for similar reasons (H.F. Searles, "Psychoanalytic Therapy With Borderline Patients—The Development, in the Patient, of an Internalized Image of the Therapist," paper presented at Temple University School of Medicine, Philadelphia, April 25, 1980). He argues that borderline patients need to be able to identify some aspect of their transferences (e.g., sadism) in the therapist and that the therapist needs to be comfortable with these transference characteristics before the patient can be comfortable with them. This cannot occur if the therapist interprets transference early in the therapy.

Gunderson (20) cautions the therapist against either colluding with the patient in legitimizing his or her anger or interpreting too quickly that this anger is disproportionate and unrealistic. He recommends that the transferential bases of outbursts of rage and the circumstances in the patient's current environment which trigger these reactions should be explored. While Gunderson believes that the borderline patient's excessive aggression probably reflects a mixture of reaction to the environment and drive factors, he deems it most useful for the therapist to treat such rage as reactive in order to encourage the patient to identify angry outbursts as symptomatic—that is, as maladaptive and potentially modifiable responses to specific sets of circumstances and perceptions. In this respect, Gunderson steers a middle course: he calls for early exploration of the roots of negative transference phenomena without much early interpretation.

Providing Corrective Experiences in Therapy

The concept of corrective emotional experience was most extensively developed by Alexander (30). Subsequently, psychoanalytic theorists have recoiled from stereotyped notions of the therapist as someone who contrives to behave in ways designed explicitly to counteract the patient's experiences of bad parenting and in this way effects a "cure." Such strategies are thought to be overly simplistic and to demean the intellectual rigor of the therapeutic endeavor. Nevertheless, most of those who write about intensive psychotherapy with borderline patients agree that an essential part of treatment involves providing growth-enhancing experiences which these patients have not previously had. There is disagreement about whether these new experiences are available to the patient inherently in a classical psychotherapeutic framework or whether the therapist must go out of his or her way to structure new experiences for the borderline patient. Kernberg (31), whose view of treatment is most "classical," writes about the importance of the therapist's tolerating the patient's expressions of intense ambiva-

lence. As the patient sees that the therapist does not crumble under the patient's aggressive onslaughts, the patient's fears about his or her own impulses diminish, and integrative ego functions are strengthened. Boyer (10) agrees with Kernberg and goes on to caution that the therapist's role should not include providing the real experience of good parental caretaking to substitute for presumed poor past life experience. For example, Boyer questions the need for the therapist to be available to borderline patients for emergency contacts between interviews. Rather, he states, "The best substitute parenting one can afford the patient is to hew as closely as possible to the classical analytic model."

By contrast, Buie and Adler place considerable emphasis on actively providing the patient with new experiences, especially in the later phases of treatment when testing and acting out have diminished. They maintain that "the capacities to know, esteem, and love oneself can be developed only when there is adequate experience of being known, esteemed, and loved by significant others" (8, p. 77). In treatment this translates into a process that they call "validation." The therapist works to underscore the reality of the patient's positive qualities by reacting with "appropriate subtle expressions of esteem" to the patient's accounts of positive experiences, conveying that these qualities have registered in the therapist's mind as realities. This allows the patient not only to feel the realness of these qualities but also to gain, through introjection and identification, the capacity for self-validation and greater capacity for autonomous self-esteem. Buie and Adler caution that in order for this validation process to be effective, the therapist must genuinely esteem (and even love) the patient. While most therapists would agree that treatment must be based on mutual respect, few writers so explicitly weave countertransference elements into their theories of therapy with borderline patients.

Masterson likewise advises the therapist to be a "real person" and actively support the patient's individuation by maintaining and communicating the consistent expectation that the patient will act in a realistic, healthy, mature fashion: "This extends as far as congratulating the patient for realistic achievements, empathizing with his realistic defeats and disappointments" (7, pp. 90–91).

Masterson also writes of a process that Mahler has termed "communicative matching" and that Masterson sees as an essential part of the working-through phase of treatment. According to Mahler's (32, 33) description of the separation-individuation process in infants, the toddler in the rapprochement phase insistently returns to the mother for "emotional supplies" after wandering off to explore the world. The mother who provides these supplies by responding to the child's activities in such a way as to approve of his or her further individuation is engaging in communicative matching. Masterson (7) posits that this developmental experience has been minimal in the borderline patient and that it is the therapist's job in the latter part of treatment to provide such an experience. This is done, for example, by discussing with patients their new feelings or interests, such as sports, the stock market, or the etiquette of dating. In these discussions, the therapist uses his or her own knowledge in a self-disclosing and educative manner to help the patient develop and reality test these new interests. In this way, the therapist supports the patient's newly emerging self and furthers the process of differentiation.

Gunderson's stance on the issue of corrective experiences is similar to that of Masterson, Buie, and Adler. He writes that once behavior has been controlled, the borderline patient's identity disturbance is best modified by noninterpretive work. Specifically, Gunderson sees the therapist's role as one of supporting the importance and validity of the patient's new ideas and feelings that emerge in treatment as well as actively validating the patient's growing awareness of the complexity of his or her personality (20).

Of all the authors who write on this subject, Chessick (15) attaches the most importance to experiential factors in the treatment of borderline patients. He notes that much more is internalized by the patient than the healthy experience of a correct interpretation. The patient comes to identify with many of the therapist's characteristics, including a nonanxious, observing attitude, refusal to be manipulated, and a sense of taking active responsibility for his or her own actions and emotions. Chessick notes that at the height of the transference, it matters little what the therapist says: "The patient is not interested in the *words* at all, any more than when the mother picks up the baby, the baby cares which lullaby the mother is singing" (15, p. 179).

DISCUSSION

The authors discussed here are all guided by the basic technical principles noted in the first section of this paper, yet their techniques diverge on many important issues. How are we to account for the fact that these highly experienced clinicians claim success in using different strategies to treat borderline patients? The following factors may be relevant in considering this question.

Different Views of What Constitutes Borderline Pathology

Most authors argue that their therapeutic techniques are based on their particular concepts of the nature of the borderline patient's psychopathology. For example, both Kernberg and Masterson subscribe to what are essentially models of conflict. Kernberg sees the borderline individual as using primitive defenses to keep apart contradictory images of self and others in an effort to protect positive introjects from being overwhelmed by negative, hostile ones. Masterson's "rewarding" and "withdrawing" part-objects are like-

wise oppositely valenced introjects, which in Masterson's scheme must be kept rigidly separate to preserve the illusion of symbiosis with the mother and to ward off abandonment depression. Both of these writers deem verbal intervention to be the most powerful tool in bringing about insight and change in borderline patients.

At the other end of the spectrum, writers such as Buie, Adler, Chessick, and Giovacchini see borderline psychopathology as consisting in large part of deficits in ego structure—particularly in the development of stable mental representations of helpful persons and experiences. They argue that these structural deficits leave the borderline patient incapable of using verbal interventions. In therapy, deficits are repaired through the creation of a holding environment in which experiential learning can take place.

There is a correspondence between what these authors see as the core of borderline psychopathology and what they deem to be the core of therapeutic technique. Those who emphasize the centrality of intrapsychic conflict claim that interpretation is the most important means of bringing about basic and lasting change. By contrast, those who emphasize the borderline patient's deficits in intrapsychic structure argue that experiential learning within a holding environment is the crucial element in helping patients develop the ego structures they lack and that interpretations cannot be "heard" until the necessary intrapsychic structures are in place.

Distinct Patient Populations

The term "borderline" is often used so broadly that the range of patients included under this diagnostic umbrella is very wide with respect to the type and severity of psychopathology (15, 34–36). It may be that patients sort themselves out and that each of the writers I have discussed ultimately establishes working relationships with different subgroups of borderline patients on the basis of a good "match" of personalities and technical approaches. For example, the differing views that have been set forward regarding work with positive and negative transference may reflect differences in the patient populations studied. Patients whose pathology involves considerable paranoia and hostility might be more likely to respond to an approach that highlights these feelings interpretively than to an approach that emphasizes the patient's longings for holding and soothing. Similarly, patients whose ego structures are less well defined and who initially rely more heavily on the therapist to support adaptive ego functioning might be more inclined to respond to interventions that emphasize experiential learning and role modeling than those that are primarily verbal and centered on conflict.

The idea that patients sort themselves out in a matching process would be consonant with the empirical finding that the vast majority of borderline patients do not complete psychotherapeutic treatment and that those who do successfully complete treatment are likely to have had previous contacts with other psychotherapists in treatments which did not last (18).

Variations in Therapists' Personalities

Little has been written about the ways in which the therapist's characteristic mode of relating to others affects the course and outcome of treatment with borderline patients. Character traits obviously cannot be taught and so represent a problem for those who would try to formulate methods of treatment that any properly trained professional can use.

Even more troublesome is the issue of the extent to which the psychotherapist's own psychological makeup determines his or her view of the nature of psychopathology. The idea that highly personal intrapsychic determinants influence a psychodynamic theorist's concepts of mental health and illness is logical (37) but also threatening, for it calls into question the belief held by many psychodynamic therapists that they are engaged in the formulation and practice of a science.

Yet one cannot read writers like Kernberg, Masterson, Buie, and Adler without noticing the striking correspondence between their theories and personal styles. Kernberg's tone is confrontational; his interventions are sharp and he seems personally eager to meet the challenges of his patients' hostility and paranoid projections. His emphasis on the need to focus on negative transference and conflict pervades the treatments about which he writes. By contrast, Masterson's tone is parental, and his technique involves a certain amount of coaching. He sees his task in part as creating a better parenting experience for his patient and providing the patient with a role model on which to base new, healthier introjects. Buie and Adler are less confrontational; their styles might generally be described as more warm and giving than that of Kernberg, and they emphasize their patients' longings for a perfect caregiver and the need to allow positive feelings for the therapist to emerge and flower. It seems obvious that these approaches are likely to resonate differently with different patients, depending on the patients' levels of object relatedness and specific defensive styles.

Emphasis on Different Facets of the Same Treatment Process

Each writer strives to display prominently those ideas which distinguish him or her from others in the field. Thus, discrepancies in technique may be more salient on paper than in the consulting room. For example, it appears that most authors use a mixture of interpretive and holding techniques early in therapy. Buie and Adler employ confrontation and interpretation early on, but they see these interventions as serving to create and maintain a holding environment. Conversely, Kernberg admits the importance of the

therapist's holding functions early in treatment, since they enable the patient to hear interpretations. Frosch (38) recommends a mixture of supportive techniques to help the patient overcome ego defects and interpretive techniques to elucidate conflicts and pathological defenses. If one looks closely at the clinical practices of psychodynamically oriented therapists, such a mixture appears to be the norm in treating borderline patients (6).

The different degrees of importance that these writers attach to work with negative and positive transference may likewise reflect emphasis on different phases of treatment. Kernberg's writing about technique focuses heavily on the early period of psychotherapy, when the relationship is typically most tenuous and stormy. By contrast, the writings of Masterson, Buie, and Adler devote proportionately more attention to the later phases of the therapeutic process, when there is generally more collaboration between patient and therapist.

One final hypothesis is worth considering. It may be that these therapists achieve good results by using different methods because the therapeutic action of their interventions is based on factors other than those which they believe effect change—factors which are common to all of their techniques but which have not yet been identified. We still have much to learn about how psychotherapy works.

Current clinical use of the borderline diagnosis encompasses a spectrum of psychopathology, and different patients within this spectrum probably require different therapeutic techniques. It is therefore incumbent upon those who study borderline patients to determine which particular psychopathological constellations are amenable to which specific interventions. We would also do well to examine more closely the process by which patients and therapists are "matched" according to the therapist's techniques and the patient's and therapist's respective personality styles.

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Control Groups for Psychosocial Intervention Outcome Studies

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In psychosocial outcome research, as contrasted to pharmacologic research, control groups receiving inert treatment, designed to raise expectations but otherwise provide no service, are almost never indicated; this is true because of methodologic as well as ethical reasons. Four types of comparisons suffice as alternatives: treatment versus no treatment, treatment versus minimal treatment, treatment A versus treatment B, and dismantling. When choices are made among these types of comparisons with power analysis and eight other factors taken into account, the questions of outcome research should be answerable with maximum economic efficiency, with maximum benefit to subjects, and without deception.

(Am J Psychiatry 1987; 144:275–282)

Researchers in pharmacology have made widespread use of placebo control groups. When patients take drugs they also experience a variety of psychological effects, many of which can be positive: for example, relief of fear, increased hope, relief of conflict about whether to obtain treatment, direction of attention toward positive aspects of one's condition, and unconscious attempts at improving one's condition in order to preserve one's faith in the treatment. These can produce powerful and lasting positive effects (1, 2). It is almost always worthwhile to separate the biologically mediated drug effects from psychologically mediated effects, and placebo control groups are accordingly often used.

This paper will critically examine how such reasoning should or should not be extended to nonpharmacologic interventions, such as psychotherapy or psychoeducational interventions. The necessity for something analogous to a placebo drug in psychosocial outcome research has become widely accepted; most often the placebo analogy is attempted by some procedure that is meant to appear to the subject as if it ought to be useful but that is in fact meant to be useless, or inert. Landman and Dawes (3) have stated that "placebo controls are by this time standard procedure in the evaluation of psychotherapy outcome. Placebo control groups permit the specification of the contribution of so-called placebo effects: the beneficial effects of theoretically nonspecific or theoretically inert factors such as attention, expectation, or suggestion." But among careful methodologists a consensus on the necessity for comparison groups receiving inert treatment is far from established. Wilkins (4) concluded that "in addition to creating an ethical dilemma, the continued use of placebo groups actually interferes with the accumulation of information about the effectiveness of therapy procedures." O'Leary and Borkovec (5) stated, "Because of problems in devising a theoretically and practically inert placebo, we recommend that the term *placebo* be abandoned in psychotherapy research." Kazdin (6) stated that "Actually, control for treatment credibility is required only for a small portion of research questions that are of interest to outcome investigations."

What sort of comparison group strategies are most logical, ethical, and efficient in psychotherapeutic and psychoeducational research? It is obvious that the well-being of many subjects and the interpretability of many studies are at stake in arriving at the best answer to this question. What is not so obvious is that, for reasons to be pointed out later, the saving of literally millions of dollars of research money is also at stake. In a time of scarce research dollars, this consideration demands our attention.

Before attempting to construct the most logical strategy for decisions on comparison groups, let us designate two related methodologic questions not at issue. The necessity for some sort of comparison group is not under contention, at least with respect to all the designs under consideration here, for reasons well explained by Campbell and Stanley (7). Second, the need for measurements carried out under blind conditions is similarly not at issue. Placebo control makes it

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Supported in part by New Investigator Research Award MH-41127 to Dr. Strayhorn from NIMH.

The author thanks Jacob and Patricia Cohen and Joaquim Puig-Antich for their reviews of this paper.

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easier and more convenient to keep raters blind, but blind ratings can be obtained with or without placebo control and constitute a separate issue.

HOW USEFUL IS THE PLACEBO ANALOGY IN PSYCHOSOCIAL RESEARCH?

In deciding how much we wish to extend the placebo strategy from drug research to psychosocial research, let us focus in turn on four sets of issues: the conceptual issue of the distinction between "specific" and "nonspecific" treatment; the ethical issues involved in giving placebo treatment; the validity of assumptions about the equality of so-called nonspecific factors; and the validity of assumptions about the inertness of so-called inert treatment.

Conceptual Distinction Between "Specific" and "Nonspecific" Aspects of Treatment

The term "nonspecific factors" may seem to communicate something concrete until we actually try to define that something. Some authors (8, 9) spoke of nonspecific factors as those components "present in all forms of treatment" or "part of every procedure." But the elements we would like to refer to as common factors—expectations for success, trust in the therapist, increased morale, knowing that one is understood, being motivated to try more adaptive ways of living—are aspects that vary quite considerably, even within cases carried out by the same therapist using the same brand of therapy. When we speak of what is common to all therapies, if we mean that which is universally present in every therapeutic transaction, almost nothing is nonspecific. On the other hand, if we mean that which can sometimes occur in some therapy other than the one in question, then almost everything is nonspecific.

Nonspecific treatment, as noted by Wilkins (4) and O'Leary and Borkovec (5), is that which the researcher is too ignorant to specify. As Kazdin (10) has pointed out, if there are factors powerful enough to favorably influence subjects' outcome, such ignorance should be attacked: such factors should be specified, operationally defined, and manipulated consciously. The degree of confidence in the treatment that the therapist communicates, the warmth of the therapist's tone of voice, the degree of approval for subjects' improvement, the enthusiasm the therapist communicates about the usefulness of the intervention—all these are subtle factors but ones that may be specified and measured nonetheless.

A second means of defining what we are trying to control for with placebo groups was set forward by Rosenthal and Frank (1). They pointed out the impossibility of providing inert psychotherapy but suggested defining placebo treatment in terms of the researchers' theory: "participating in an activity regarded as therapeutically inert from the standpoint of the theory of the therapy being studied." Such language may be confusing. If, as the evidence indicates (3), placebo groups usually have positive effects, how can we call then inert according to some theory unless that theory is clearly wrong? What is really desired of a placebo treatment is that the treatment, according to our best theory, be active with respect to one mechanism and inert with respect to another. For example, traditional active drug versus placebo designs most often really include no treatment package that, as a set of elements, is inert. For one group, the treatment consists of a pharmacologic influence and a set of psychological influences; for the second group, the treatment consists of the psychological influences only.

Examining those semantic issues allows us to see more clearly that in psychosocial outcome research, so-called placebo control pits one set of psychological influences against another set of psychological influences. For example, the intervention under study may consist of exposure to an empathic person, twice a week, who appears confident, speaks in a gentle tone of voice, raises a certain set of questions, and delivers a certain set of instructions; the control procedure may consist of a package in which all these elements except one are the same, and one of particular interest is different. Which are specific and which are nonspecific? The decision as to what influences are to be tested and which are to be controlled for is a decision that depends on the specific goals of the study and not on a routine, predetermined methodologic prescription.

Ethical Considerations

In the ethical arena, also, it is hazardous to make blind generalizations from drug research to psychosocial outcome research. While placebo control in drug research seldom necessitates deceiving subjects, a psychosocial treatment designed so as to be inert often requires some deception, or at least a withholding of important information without the consent of the subject.

In a drug study, it is very clear to most subjects what is meant by an inert pill. Because the placebo pill is visually indistinguishable from the active pill, the experimenter is free to be open about the fact that some pills are active and some pills are inert. Subjects are informed that the identity of the drug they are getting will be withheld from them, and if they do not consent to this arrangement, they are free not to join the study. An important precedent is at stake: the precedent that the clinician should not deliberately withhold the information necessary for the patient to make an informed decision about accepting the treatment. The subject's full consent to the withholding of information allows the drug study to take place without undermining this precedent. Almost never, however, is a psychosocial intervention visually indistinguishable from an inert comparison treatment. This implies that the withholding of information about

which treatment is inert must occur within the context of the communication between the experimenter and the subject. It is much more conceivable that a subject could later say, "If I had known all that you know about this treatment, I never would have accepted it." The precedent for open and honest communication is more clearly endangered.

An example of a psychosocial treatment carefully designed to be inert is provided by Lent et al. (11), who called their placebo treatment "subconscious reconditioning." Subjects with phobias were informed that they would be presented "anti-fear" messages at subliminal levels by a tachistoscope. In fact, the messages were nonsense syllables. This procedure seemed to produce credibility ratings equal to that of systematic desensitization. It would have been possible to carry out this experiment in a way that involved no withholding of important information without subjects' consent, for example by telling subjects that there were two treatments, that the nature of the treatment other than the one they got would be withheld, that one of the treatments was designed to be inert, and, for the control subjects, that the syllables that were flashed on the screen might or might not be anti-fear messages. It is seldom that an experimenter goes to such lengths, however. A study couched in such disclosures would probably be less credible to subjects. Furthermore, the notion of an interaction designed to be useless seems to arouse negative emotions in subjects not aroused by the notion of an inert pill.

What occurs much more often in actual practice is that the so-called placebo treatment is not hypothesized to be totally useless but simply less helpful than the experimental treatment. Examples of such treatments might be listening empathically as patients talk about whatever subject they choose or playing board games with children in a kindly manner. Here the experimenter can honestly say that either treatment may be expected to provide some benefit. But such comparison treatments are not inert, and it muddles our thinking to call them placebos. Instead, they constitute what I will later call "minimal but useful" treatment control groups, or perhaps "treatment A versus treatment B" comparisons.

Validity of Assumptions About the Equality of Nonspecific Factors

If we return temporarily to the traditional but vague language of specific and nonspecific factors, and if for the sake of simplicity we ignore interaction effects, we can express the rationale for a placebo group in the following equation:

$$\text{Observed Difference} = \text{Specific(A)} + \text{Nonspecific(A)} - [\text{Specific(P)} + \text{Nonspecific(P)}]$$

In words: the observed difference between the two groups is the sum of the specific and nonspecific effects of the active treatment group minus the sum of the specific and nonspecific effects of the placebo group. The variable we are interested in solving for is the specific effects of the active treatment. We cannot obtain a unique solution to this equation unless it has only one unknown. To meet this condition we make certain assumptions: we assume that the nonspecific effects of active treatment and placebo are equal and thus cancel out of the equation; we assume that the specific effect of the placebo is zero, as the researchers intended it to be. If such assumptions hold, then the observed difference between the groups equals the specific effect of the active treatment.

How valid is the assumption that the placebo treatment and the active treatment generate equal expectancies, hopes, increase in morale, and the other effects called nonspecific? Again, it is impossible to leap blindly from drug research to psychosocial outcome research. Empirical research has shown that in behavior therapy, treatments and control procedures do differ in their abilities to raise expectancies of improvement (12–14). Thus if group A improves more than group P, it could be that treatment A is simply a better placebo than treatment P. Some methodologists have advocated circumventing this problem by trying to measure expectancies of improvement; the trouble with this strategy is that expectancy of improvement is only one of a set of variables that the placebo group is intended to control for: there are also the soothing effect of interpersonal support, the arousal of the wish to please the experimenter, and others.

Validity of Assumptions About the Inertness of the Control Group

The equation presented earlier also requires for a unique solution the assumption that the specific effects of the purportedly inert treatment are zero. Suppose our purportedly inert treatment actually has positive effects; we could in this circumstance observe no difference between the two groups and falsely conclude that our intervention is useless. On the other hand, if our purportedly inert treatment actually has harmful effects; and if our active treatment is useless but nonharmful, then we could observe a difference between the two groups and falsely conclude that the active intervention is useful.

Again, the situation in psychosocial research is different from that in drug research. We can be fairly sure that our placebo pill is pharmacologically inert if we give a substance that represents a minute quantity of something present in much larger quantities in the diet of all subjects, for example, or if we give a small quantity of something that is not absorbed from the gut.

One major difference between drug studies and psychological intervention studies is that there is no such thing as "generic" contact with an intervening agent. A person who is attempting to carry out a placebo intervention must fall somewhere on the spectrum between kind and cruel, between understanding

and insensitive, between saying wise things and saying unwise things, and so forth. Unless we are prepared to argue that medieval torture chambers were therapeutic, we must reject the idea that any and all sorts of contact with another human being must have therapeutic effects. Those who construct "attention-only" control groups must specify a certain sort of activity or interaction to take place during the contact. And the validity of the equation presented earlier depends on the specific effects of this sort of contact being not helpful, not harmful, but zero. The task of supporting this assumption is a task approximately as difficult as our original task of quantifying the effect of the intervention in question.

Adding a third group to the study, a no-treatment group, in no way solves this problem. If the placebo group does not differ from the no-treatment group, it could be that the so-called placebo treatment was really active, with harmful effects, and these were counteracted by the effects of positive expectancies to yield net effects of zero. The treatment group could appear superior to both groups purely because it was better at raising morale and building expectancies; thus the "placebo" effect has not been ruled out as an explanation for our observed differences.

To summarize thus far, comparison group considerations for psychosocial outcome research differ from those for drug research in at least four ways: it is a more individualized decision which elements and mechanisms are to be tested and which are to be controlled for; inert treatment is much more difficult to arrange without deception; it is much more difficult to establish that expectancies and credibility and other so-called nonspecific effects are really equal for the two groups; and it is much more difficult to establish that the comparison treatment is really inert in the desired respects.

If we cannot make blind analogies between drug research and psychosocial outcome research, what then is the best way to arrange comparison groups for psychosocial outcome research? The following sections will address this question.

THE PROPOSED SOLUTION

The enterprise of psychosocial outcome research can be carried out ethically and efficiently, at all stages of the maturation of an intervention, with four types of comparisons. The entire enterprise can be carried out without purposely useless treatments or withholding of important information.

Comparison 1: No-Treatment Control Groups

In the first type of comparison, the experimenter simply treats one group, withholds treatment from a second group, and compares the results. If the time of treatment and follow-up is short enough, treatment may then be offered to the control group; the waiting-list control group is one example of such a comparison.

The no-treatment comparison obviously does not try to do everything at once. It does not differentiate at all among portions of the treatment package. If, for example, we get positive results, in a no-treatment control study, from having warm and empathic therapists do cognitive therapy, we do not know that we would not have gotten equally good results from having warm and empathic therapists do financial counseling. However, we have accomplished a very important task: we have injected our intervention into a pool of treatment packages that have evidence of being useful for the outcome variable we are trying to influence. We have left specific and nonspecific elements lumped together; all elements are considered part of the package. The attribution of the effects to the raising of morale is in no way ruled out.

Comparison 2: "Minimal But Useful Treatment" Control Groups

An example of this procedure would be one in which the experimental group subjects receive individual sessions in which they are taught a cognitive technique, and the control group subjects are given a book describing some self-help procedures previously found to be useful. Or the parents of experimental children go through an extensive training procedure, and the parents of control children are shown a useful videotape on parenting. Or systematic desensitization is compared with giving subjects a pamphlet telling how to carry out the desensitization procedure on themselves. Or therapy is compared to allowing patients to call and arrange to receive some support as they consider necessary. The minimal but useful treatment control can carry out its purpose without any need to make the number of hours of contact identical between the two groups or to arrange for identical expectancy of benefit. All that is necessary is that whatever effects the comparison procedure does have should be, on the average, positive.

This type of comparison shares many aspects with the active versus no-treatment comparison. There is no attempt to identify the relative effectiveness of various components of the treatment package. Positive results on our comparison inject the treatment into a pool of interventions with evidence for usefulness. The inexpensive treatment provides something that is likely to be of some benefit to the control group; thus recruitment of subjects and relations with control group members are improved. The more useful the minimal treatment proves to be, the more this comparison resembles the next one on our list, the treatment A versus treatment B comparison.

Comparison 3: Treatment A Versus Treatment B

The first two types of comparisons cast interventions into a pool of candidates. The third type conducts a

"runoff" among two or more of them, in their full elaboration. In this type of comparison there is still no attempt to differentiate among the elements of the packages. If treatment A works better than treatment B, it could be because treatment A generates greater expectancies that overshadow treatment B's superiority in all other ways. If treatment A replicably works better than treatment B because it generates higher morale and expectancy among subjects, it should be chosen in real-world applications as long as those conditions hold; the "applied" research question is what works better, not which aspect is responsible.

Comparison 4: Dismantling

The final type of comparison attempts to resolve our ignorance about particular components of the treatment package: this is the "dismantling" experiment. Here there are groups that differ only with respect to one element of the package or one set of elements. The difference between the two groups, if proper experimental conditions are present, can be attributed to the elements not in common. That is, the experimental group involves, for example, elements X, Y, and Z; the control group involves only elements Y and Z. The active drug versus placebo comparison is actually a special case of a dismantling study.

CIRCUMSTANCES FOR APPLICATION OF THESE FOUR COMPARISONS

What is the optimum strategy for deciding which of the four types of comparisons to use in a given study? The best answer to a given study is dependent upon several considerations, including 1) power analysis issues, 2) the strategy for optimum economic efficiency, 3) the accumulated evidence for the effectiveness of treatment A, 4) the accumulated evidence for the effectiveness of an alternative treatment, 5) the accumulated evidence on the nonresponsiveness of the target variable to certain treatments, 6) the degree of specification possible for the treatments and the sample, 7) the risk and expense and theoretical importance of some element or set of elements in the treatment package, 8) the degree of actual and perceived urgency of intervention versus no intervention, and 9) the duration of treatment and follow-up.

Power Analysis Issues

The first two types of comparisons mentioned earlier, i.e., with no-treatment control groups or minimal treatment control groups, are far less expensive than the third and fourth types, i.e., treatment A versus treatment B and dismantling. One reason is that no treatment or minimal treatment obviously costs less to deliver—but this is not the main reason. The main reason has to do with the number of subjects required to obtain the desired power for the comparison—that is, the need to have enough subjects to reject a false null hypothesis. The overriding principle of power analysis is that as the differences between groups become smaller, we need a greater sample size to have a good chance of detecting the differences at a statistically significant level. The more active and effective the comparison treatment is, the smaller is the expected difference between the two groups and the greater is the number of subjects needed.

For example, suppose one considers the warmth of the therapist as something to be controlled for and considers a set of instructions delivered by the therapist as the procedure whose effect is to be estimated. Suppose that in reality, the instructions are useful and add materially to the success of the therapy; suppose also that a fairly large portion of the effect is accounted for by the warmth of the therapist. Cohen (15) quantified what behavioral scientists usually regard as a small, medium, and large effect size, defining these as a difference between two groups of 0.2, 0.5, and 0.8 SDs, respectively. Suppose that in our hypothetical experiment, the warmth of the therapist in nondirective conversation is a potent enough intervention to produce a medium effect size, a 0.5-SD increase in our outcome variable score as compared to no treatment. Suppose, furthermore, that the specific instructions, when added to the therapist's warmth, constitute a more potent intervention, able to produce a large effect size, 0.8 SDs when compared to no treatment. (These hypothetical parameters are not unreasonable, given the results of meta-analyses of psychotherapy outcome studies [3, 16, 17].) Unless the specific procedure is particularly costly or risky, one would, according to this information, certainly consider the specific procedure a useful addition to the package, since it increases the effect size from medium to large.

But when the two interventions are compared with one another, the difference between them is only 0.3 SDs. How many subjects are required if there is to be a conventional 80% chance of detecting a 0.3-SD difference? If we set alpha equal to a conventional .05, the tables of Cohen (15) reveal that 175 subjects per group are needed: that is, a total of N of 350 subjects. To compare the more potent procedure to a no-treatment group with zero effect, so that our effect size is 0.8, would by contrast require only 26 subjects per group, for an N of 52. Thus our active–active comparison requires nearly seven times as many subjects as does our active–no-treatment comparison. If a course of therapy costs $1,000 per patient, our decision to control for warmth entails spending an extra $324,000. The extra cost comes not so much from having to treat the original no-treatment control group (a comparatively paltry $26,000) but from the increased sample size called for by our power analysis.

In general, then, the critic who says, "You should control for these nonspecific factors," should simultaneously be arguing, "Your research budget should be vastly increased."

Why is this point not more obvious among the

research community? Critics of research design have purchased the luxury of insisting upon control for various nonspecific factors at the price of simply ignoring power analysis. Cohen (18) in 1962 documented the fact that a large portion of published research ignored the necessity for sufficient sample sizes to reject a false null hypothesis. Examples still abound. The interested reader may, for instance, refer to some papers suggesting that biofeedback is not significantly better than progressive relaxation for tension headaches (19–23); in these studies cell sizes typically ranged from six to nine. With such sample sizes differences would have to be huge in order to reach statistical significance.

The Issue of Efficiency and Accumulated Evidence for the Effectiveness of Treatment A

What is the way to approach treatment outcome studies so as to use no more and no fewer subjects than needed, so as to maximize economic efficiency and the benefit delivered to subjects?

The question is in some ways analogous to a mathematical puzzle: if one is permitted only to ask yes or no questions, what is the most efficient way to identify a particular integer between, say, 1 and 100? The most efficient strategy is to ask questions that eliminate half of the remaining alternatives each time, with the first question being, "Is it greater than 50?" In adopting this strategy, one totally precludes the possibility of getting the correct answer on the first question but guarantees getting the correct answer on the eighth question. To start with a first question of "Is it 19?" gives a chance of solving the problem at one shot, but if this attempt is not successful, the cost in terms of wasted guesses is high.

Similarly, when a new intervention package is being tried, one could design a study in which there are multiple groups meant not only to test whether specific factors have an effect over and above nonspecific factors, but also to test how the particular elements contribute differentially to the outcome. However, by the reasoning in the previous section, such an experiment is very expensive. If the innovative treatment package proves ineffective, the research on the differential contribution of the elements would most likely be wasted. It is more efficient first to test whether the new intervention, as a package, is useful—that is, whether it has an effect when compared to something of minimal or zero effect. In other words, the newness of an intervention tends, all others things being equal, to call for no-treatment or minimal but useful treatment control groups. Many innovative interventions will be eliminated at this first step. As an intervention proceeds along the series of steps from "innovative" to "tried and true," granting agencies should find it more and more reasonable to invest the larger amounts of money required to determine how the intervention compares with other full-blown interventions or to determine how the specific elements of the package contribute to its usefulness. Thus in the most efficient strategy, the design of an outcome study should be predicated on the degree to which the proposed intervention has been seasoned by previous studies.

Fortunately, the dictates of ethics are in this respect consonant with the dictates of efficiency. When an intervention is new and untried, we can truthfully tell subjects that we are not sure whether it works better than no treatment or minimal treatment; as it becomes more seasoned and such statements become dishonest, we no longer need such comparisons but need instead to compare our treatment with other contenders or to dismantle it.

Accumulated Evidence on the Effectiveness of Treatment B

The more sure we are that an effective treatment exists for our target condition, the more we should tend to use that treatment as the standard of comparison for other treatments, especially if the condition is one that is severe or disabling. For example, since there are effective treatments available for depression (24), the state of the art in this field calls more for A versus B comparisons; since there is less evidence for effective intervention for preventing recidivism in criminals (25, 26), the state of the art in this area would propel us more toward no-treatment or minimal interference comparisons.

At this point in the reasoning process we encounter a problem. Once there is a standard useful treatment available, how are innovative treatments to enter the field of contenders? It is unethical in such a circumstance to use no-treatment groups, but the innovative treatment may not be thought worthy of the expenditure necessary for a large-scale comparison with the standard.

The solution is supplied by the fact that we can have a fairly inexpensive treatment A versus treatment B study if we are interested purely in ruling out *large* differences between groups, leaving to further research the task of more precisely comparing the treatments. For example, suppose that there is a standard useful treatment for a condition. Suppose one assembles 52 subjects into two groups and compares the standard treatment with our innovative treatment. If significant differences are not found, there is no greater than a 20% chance of a *large* difference between the two groups. These results have the same effect as do positive results in our first and second types of studies: they inject the innovative treatment into a pool of contenders. They indicate that more subjects should be enlisted to further test the innovative treatment against the standard treatment.

Accumulated Evidence on the Nonresponsiveness of the Target Variable to Certain Treatments

If the target variable is clearly refractory to certain elements of treatment, then to criticize a study of that

target variable on the grounds of failure to control for those elements is to advocate waste. For a clear-cut example, consider a study of microsurgical techniques for reattaching severed limbs. Surely no one would criticize such a study for failing to provide a placebo group, and not only for ethical reasons: it is obvious that suggestion and attention from and contact with an empathic person, when taken by themselves, do nothing for the condition of a severed limb. Our a priori knowledge is sufficient for us not to need to prove this fact over and over again in each study conducted.

Certain psychological conditions approximate this situation. Repeated and habitual suggestion and antisocial behavior constitute one of them. If, for example, a study showed that a certain procedure greatly reduced recidivism in violent adult criminals when compared to a randomly assigned no-treatment control group, a reviewer who dismissed this study for lack of a placebo control group should be censured for wasteful pettiness. There have been enough studies failing to find effects of several active or placebo interventions (25–27) that to require placebo control, as compared with no-treatment control, for this particular target variable is to beat a dead horse. By contrast, a transient increase in self-reported satisfaction or a transient decrease in self-reported pain is much more possible to produce in the patient by a variety of morale-raising procedures (28), and here our critic would be on solid ground.

Degree to Which the Population and the Treatment Can Be Specified

A problem with the treatment A versus treatment B design is as follows. Suppose that treatments A and B have been found in prior research to be useful when compared to minimal interference. Now an investigator compares them and, with a sufficient number of subjects, finds no significant difference, demonstrating that the difference in their effects is highly likely to be only trivial. The researcher would like to conclude that they are approximately equally effective. The question is, are they equally effective or are they, in the hands of this researcher, equally ineffective? There are dozens of ways that interventions can be rendered useless: using them with a population for whom they are not suited, using them in too small a dose, using them without consideration of important interpersonal factors, and so forth.

One possible solution to this dilemma is to add a no-treatment or minimal-treatment group to the design so as to simultaneously establish that both treatments are equally effective rather than that both are equally ineffective. This solution should be avoided if possible, since such a design is more costly and since it is much more acceptable to subjects to know that they will be assigned an active treatment. The two-group design is sufficient to the degree that past research on the effectiveness of treatments A and B can be generalized to the present study; in turn, those conditions hold the more the minute details of the treatment have been clearly specified and the more the treated population has been accurately described. In other words, the more specifically the subject populations and the treatments have been described, in past studies and in the present one, the more we can avoid having to start each study as though we were in total ignorance. We can then more confidently use comparisons of active treatments without including no-treatment or minimal-treatment control groups.

Risk, Expense, and Theoretical Importance of Some Element of the Package

When there is some particular element in the package that is very risky, costly, or theoretically interesting, then it makes sense to use a dismantling design to quantify its effect. The use of placebo control in drug studies is really a special case of the dismantling strategy; it is almost always useful because most pharmacologic agents carry risks and costs far greater than the interpersonal maneuvers involved in drug prescription and drug taking per se, and the usefulness of a certain drug almost always has large theoretical implications. With psychosocial interventions it is necessary to be more selective about what elements are most crucial to test by dismantling. If one begins to list factors such as the intervener's tone of voice, the intervener's facial expressions, the accuracy of the intervener's empathic responses, the frequency of contact, the total length of contact, the nature of the suggestions that improvement will take place, each element of the "curriculum" delivered, and other separable elements of a psychosocial intervention, the number of potential dismantling studies is quickly seen to be astronomical. In view of the economic considerations detailed earlier, it would seem reasonable to demand at least one successful trial of a treatment package before even considering dismantling it.

Urgency of Intervention

When there is a treatment that has some evidence of being helpful for a target condition, then the more our target condition requires an urgent response, the less justification there is in using no-treatment or minimal-treatment comparisons. For example, suppose a promising innovative treatment for phobias is devised. If subjects phobic of public speaking were recruited from a group of people with no particular need to speak before groups and with no incapacity resulting from their fear, one could justify comparing the treatment to no treatment. On the other hand, if the recruited subjects were in danger of losing their jobs because of their public speaking phobias, ethical considerations would contraindicate no-treatment groups or minimal-treatment groups as a reasonable comparison; the treatment A versus treatment B comparison would be more reasonable.

Duration of Treatment and Follow-Up

Sometimes the condition clearly must be treated, but it is still possible to use waiting-list control groups, which are a special case of no-treatment controls. After the waiting time, the comparison is made, and then the control subjects are treated. This strategy is possible only when the treatment produces its effects quickly and long-term follow-up is not desired. We might use waiting-list control groups to test a quick method of reducing aggressive behavior in school children; we would not use them to test a method for long-term prevention of aggressive behavior.

CONCLUSIONS

By taking into account the variables mentioned earlier, it should be possible for researchers studying outcomes of psychosocial interventions to determine which of the four types of experimental comparisons best meets the goals of a given study and to accomplish the goals of the research enterprise without ever needing to devise inert treatments. To use such a strategy should prove beneficial with respect to ethics, efficiency, and economics.

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Use of Outpatient Mental Health Services Over Time in a Health Maintenance Organization and Fee-for-Service Plans

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The authors compared the use of outpatient mental health services in a health maintenance organization (HMO) and fee-for-service plans over a 5-year period, using data from a randomized controlled trial. In any given year, enrollees in the HMO and a fee-for-service plan with identical benefits were equally likely to visit a mental health specialist. Over several years, the HMO enrollees were about 50% more likely ever to visit a mental health specialist; fee-for-service enrollees were more likely to receive mental health care in more than 1 study year.

(Am J Psychiatry 1987; 144:283–287)

Studies suggest that the cost of providing outpatient mental health care in health maintenance organizations (HMOs) is lower than that under fee-for-service coverage and that HMOs provide such care to a similar percentage of enrollees in a given year (1–2). These studies, however, did not address differences in use over longer periods of time. If HMOs evaluated new patients at a different rate than fee-for-service care, then over time HMOs would treat a very different percentage of the total enrolled population—despite a similar annual probability of use. Over a period of several years, do participants in fee-for-service plans differ from those in an HMO in the likelihood of ever receiving outpatient mental health care? In this paper, we address this question using data from the RAND Health Insurance Study.

Such questions are important because of the high rate of enrollment in HMOs and the promotion of the HMO as a mechanism to contain medical care costs. HMOs remain a subject of controversy, especially in the area of coverage of mental health services. Critics have argued that HMOs reduce access to mental health care, especially for the chronically mentally ill.

There are several reasons to anticipate that HMOs and fee-for-service plans may evaluate new patients at different rates over time. First, some investigators have argued that HMOs may enroll healthier populations than do fee-for-service plans (3). If so, fee-for-service plans would have a higher proportion of enrollees who need longer-term care. Second, some investigators have noted that coverage of mental health services is more limited in HMOs than in fee-for-service plans (4). As a result, participants in HMOs might be less likely to receive care year after year than enrollees in fee-for-service plans, even if the health status of the enrolled populations were similar.

Virtually all previous comparisons of use of services in HMOs and fee-for-service plans focused on annual utilization patterns. Taken as a whole, these studies indicate that HMOs have similar or higher probabilities of use but lower visit rates per user than fee-for-service plans (1, 5, 6). The authors of these studies have pointed out that the conclusions about annual utilization are limited by one or more methodologic concerns. First, in each study, enrollees selected their own insurance plan; individuals who chose an HMO could have differed in health status or other factors affecting use from individuals who opted for fee-for-service coverage. Second, most studies used restricted samples (i.e., insured populations) rather than a general population including the uninsured. Third, the

Received Dec. 27, 1985; revised July 7, 1986; accepted Aug. 18, 1986. From the RAND Corporation; and the University of California, Los Angeles, Neuropsychiatric Institute School of Medicine. Address reprint requests to Dr. Manning, RAND Corporation, 1700 Main St., P.O. Box 2138, Santa Monica, CA 90406-2138.

Supported in part by NIMH grant MH-38406.

The opinions and conclusions expressed are solely those of the authors and should not be construed as representing the opinions or policy of any agency of the U.S. government.

HMO and fee-for-service benefit packages were usually not comparable, although in the study of Diehr et al. (1) they were quite similar. Any of these factors could account for some of the observed differences in use.

METHOD

The RAND Health Insurance Study is a social experiment designed to study the effects of different health insurance arrangements on the demand for health services and the health status of individuals (7, 8). In our Seattle site, participants in the study were randomly assigned to an HMO or a fee-for-service plan. The HMO was Group Health Cooperative of Puget Sound, a well-established nonprofit prepaid group practice that operated two hospitals, three mental health clinics, and 13 medical clinics in the Seattle area during the period studied (1976–1981).

HMO patients could refer themselves to the mental health clinic. The HMO had a family-system orientation and encouraged its family practitioners to manage psychiatric disorders. Two-fifths of the HMO visits to mental health specialists were to non-doctoral-level therapists, compared with one-sixth of Seattle fee-for-service visits. The fractions of visits to psychologists were similar in both systems. The HMO relied less on psychiatrists than did the fee-for-service system (30% versus 62% of visits to mental health specialists were to psychiatrists) (2).

We compared three groups of subjects. Two of the groups were random samples of the Seattle area population who were *not* enrolled in Group Health Cooperative in 1976 but were otherwise eligible for the study. The 1,213 subjects in the first group, the fee-for-service sample, were assigned to one of 11 fee-for-service insurance plans (described later in this paper). The 1,149 subjects in the second group, the HMO experimental sample, were assigned to the HMO. The third group, the HMO control sample, was a random sample of 733 members of Group Health Cooperative in 1976 who otherwise met the eligibility criteria and had been enrolled in this HMO for at least 1 year.

Those ineligible for the study included people over 62 years old at the time of enrollment; Seattle area families whose incomes exceeded $56,000 (1983 dollars) (this excluded 1% of the families contacted); institutionalized patients; military personnel and their dependents; veterans with service-connected disabilities; and patients eligible for disability Medicare and the end-stage renal dialysis programs.

Families who enrolled in a fee-for-service plan were assigned to one of several insurance plans that had different levels of cost sharing. Families in the free care plan (431 enrollees) had no out-of-pocket costs for covered services. Families with the family pay plans (506 enrollees) had coinsurance rates of 25%, 50%, or 95% for health services, subject to an income-related cap on out-of-pocket expenses up to a maximum of $1,000; beyond the cap, the insurance plan reimbursed all expenses in full. Families with the individual deductible plan (276 enrollees) had a small annual deductible ($150 per person or $450 per family) for outpatient health services, with free care beyond the deductible and free inpatient care.

The HMO experimental subjects had the same benefits as the participants in the free care fee-for-service plan. However, if the HMO experimental subjects on their own sought care outside the HMO for a service that the HMO provided, they were reimbursed only 5% of the cost. HMO experimental subjects and all fee-for-service subjects were covered for most health care services and providers, including outpatient psychotherapy up to 52 visits per year per person. This limitation effectively eliminated reimbursement for intensive long-term psychotherapy.

The HMO control subjects retained their previous coverage. With a few exceptions, they received all outpatient and inpatient care at the HMO for free. However, they paid $8–10 for each psychotherapy visit in excess of 10 per year.

Families were assigned to the HMO or fee-for-service plans by using the finite selection model (9), which balances the plans in health and demographic factors while retaining randomization. Subjects in these two groups were randomly assigned to either 3 or 5 years of enrollment. HMO control subjects were enrolled for 5 years.

Our analysis includes enrolled participants while they remained in the experiment and in the Seattle area. Data on use of HMO services were obtained by abstracting medical records (10). Data on fee-for-service plan use were obtained from claims forms filed with the experiment, which functioned as the participants' insurance company. We identified outpatient mental health visits from the mental health procedures and mental health diagnoses listed on the claims forms or medical records (11).

Our measure of mental health status was the Mental Health Inventory (12, 13), a 38-item self-administered questionnaire (or a 12-item version filled out by parents for children 5 to 13 years old). The Mental Health Inventory measures psychological distress (i.e., symptoms of anxiety and depression and loss of behavioral and emotional control) and psychological well-being during the preceding month. It has excellent reliability and construct validity (12, 13). Of note, it is a strong predictor of the likelihood and intensity of use of outpatient mental health services (14).

We used analysis of variance techniques to estimate the annual probability of use of any outpatient mental health services and of any mental health specialist (averaged over several years). For this analysis only, we used data on full person-years of participation; the person-year is the unit of analysis.

We used both nonparametric and parametric survival models to estimate the probability of use of mental health care as a function of time elapsed from

TABLE 1. Characteristics of HMO and Fee-for-Service Experimental Subjects and HMO Control Subjects

Characteristic	HMO and Fee-for-Service Experimental Subjects (N=2,362)		HMO Control Subjects (N=733)	
	Mean	SE	Mean	SE
Age (years)	25.20	0.35	26.63[a]	0.63
Family size (number of people)	2.70	0.05	2.68	0.08
Education (years)	12.8	0.078	13.8[b]	0.15
Family income (1983 dollars)	22,800	440	27,400[c]	934

[a]t=2.00, df=3093, p=.05.
[b]t=6.28, df=3093, p<.0001.
[c]t=4.33, df=1228, p<.0001.

the beginning of the study (15, 16). For this analysis we included data on all subjects who participated in Seattle, including any partial years of participation; the unit of analysis was a person. As a sensitivity analysis, we also performed an analysis of use as a function of time with only full years of participation; this resulted in no changes in conclusions. The nonparametric method used was the Kaplan-Meier or product limit estimator. This method relies on life table methods that correct for sample loss. The parametric method was a Weibull regression technique. Unless otherwise noted, the survival inference statistics reported in this paper are from the Weibull regression model.

All inference statistics are corrected for correlation in use (e.g., among family members) by a variant of Huber's method (17).

RESULTS

Table 1 summarizes the characteristics of the experimental samples (the HMO experimental sample and the fee-for-service group combined) and the HMO control sample. Although the HMO control subjects were significantly older, better educated, and had a higher mean income, they did not differ from the experimental subjects in terms of mental health status. In the experimental group, 1,200 (50.8%) were women, 53 (2.2%) were black, and 122 (5.2%) were receiving Aid to Families With Dependent Children. In the control group, 386 (52.7%) were women, 30 (4.0%) were black, and 27 (3.7%) were receiving Aid to Families With Dependent Children. There were no significant or appreciable differences among characteristics of the participants in the various experimental plans in mental health status or other characteristics (18).

Annual Use of Mental Health Services

As shown in table 2, subjects in the HMO experimental and control groups did not differ significantly or appreciably in the probability of receiving outpatient mental health care in any particular year. Subjects in the free care plan and the individual deductible plans had a significantly lower annual probability of receiving *any* outpatient mental health care than did experimental HMO subjects, but this was entirely due to a lower probability of use of general medical providers (i.e., nonpsychiatrist physicians). The annual probabilities of any use of mental health specialists by subjects in the free care and individual deductible fee-for-service plans were not significantly different from the use probability of the HMO experimental subjects.

Participants in the family pay fee-for-service plan had a significantly lower annual probability of use of both general medical providers and mental health specialists than did the HMO experimental subjects or the subjects in the free care or individual deductible fee-for-service plans (data not shown).

Use Over Time

Figure 1 provides estimates made by using the Kaplan-Meier estimator for the probability of use of any outpatient mental health care as a function of time. After 3 years, both experimental and control HMO subjects had a significantly higher probability of use than subjects in any of the fee-for-service plans—including the free care plan. The t statistics for comparisons with the HMO experimental subjects ranged from 3.3 (p<.001) for the free care plan to 5.9 (p<.0001) for the family pay plan. At the end of 3 years, 28% of the two HMO groups, 17% of the free care and individual deductible groups, and 11% of the family pay group had visited a provider of outpatient mental health care. The two HMO groups (combined for the figure) did not differ significantly in use over time (t=−0.54).

After 3 years, about 15% of the HMO groups had seen a mental health specialist, but only 10% of the free care and individual deductible fee-for-service plan groups had done so (figure 1). Although this difference is appreciable, it is not clear whether it is statistically significant. (The p values lie between .03 and .22, depending on the estimation method.) With such similar average annual probabilities of any use of a mental health specialist as shown in table 2, we would not expect to see, within 3 years, a difference as large as 15% versus 10% in the likelihood of ever visiting a mental health specialist. Such a difference would occur only if there were greater turnover of patients (i.e., more *new* patients over the years) at the HMO than in the free care fee-for-service plan.

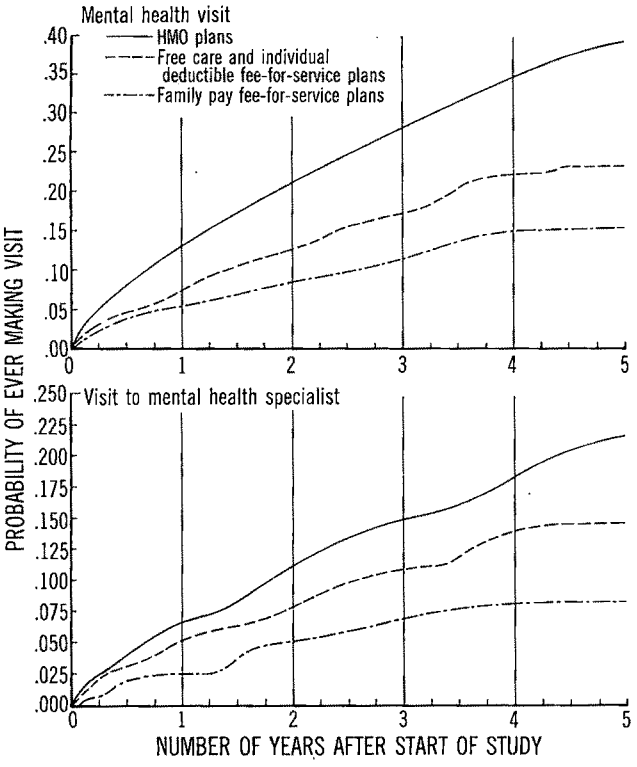
During the first 3 years of study, the average HMO experimental user visited a mental health specialist in 1.37 years, while the average free care fee-for-service user did so in 1.74 years (t=2.03, df=158, p<.05). Seventy-four percent of the HMO experimental users of mental health specialists but only 57% of free care fee-for-service users had a visit in only 1 of the 3 years (t=1.51, df=158, p<.13). (These comparisons are

TABLE 2. Annual Use of Outpatient Mental Health Services in an HMO and Fee-for-Service Plans, 1976–1981[a]

Type of Plan	Probability of Any Use					Probability of Any Use of Mental Health Specialist				
	Percent					Percent				
	Mean	SE	t[b]	df	p	Mean	SE	t[b]	df	p
HMO										
Experimental	13.9	0.94				6.5	0.70			
Control	13.2	1.06	−0.46	6467	n.s.	6.9	0.87	0.40	6467	n.s.
Fee-for-service										
Free care	9.15	1.48	−2.70	5028	.01	6.28	1.42	−0.13	5028	n.s.
Family pay	5.48	0.97	−6.24	5250	<.0001	3.25	0.80	−3.25	5250	.001
Individual deductible	7.92	1.58	−3.25	4554	.001	5.62	1.36	−0.57	4554	n.s.

[a]Standard errors and t statistics corrected for intrafamily and intertemporal correlations. Use of mental health specialist identified by mental health diagnoses recorded for visits to mental health specialists. Data include full person-years of participation.
[b]Comparison with HMO experimental response.

FIGURE 1. Probability Over Time of Ever Using Outpatient Mental Health Services in an HMO and Fee-for-Service Plans, 1976–1981



based on people who stayed in the study in the Seattle area for at least 3 years.)

The most striking differences in use over time were between the family pay plan and the other plans. After 3 years, only 6% of the family pay group had ever visited a mental health specialist, compared with 10%–11% for the other fee-for-service plans and 14%–15% for the HMO plans. Only 11% of the subjects in the family pay plan had ever visited any provider of mental health care, compared with 17% for the other fee-for-service plans and 28% for the HMO plans.

We observed no significant or appreciable differences in the mental health status at enrollment of the participants as a function of plan (the mean Mental Health Inventory scores ranged from 75.2 to 76.3 across plans; each standard error was about 0.6). Further, the differences we observed by plan in use as a function of time remained when we controlled for enrollment Mental Health Inventory scores in regression analyses. Thus, the differences in use cannot be attributed to differences in enrollment mental health status of the HMO and fee-for-service groups.

DISCUSSION

Our paper represents a first attempt to determine whether an HMO and fee-for-service plans provide some outpatient health care to a different proportion of their respective covered populations over a period of several years—that is, whether the two systems of care differ in their rate of treating new patients. Although we observed a similar average annual probability of receiving care delivered by a mental health specialist at an HMO and under identical fee-for-service coverage (the free care plan), over time HMO mental health specialists treated a significantly larger proportion of enrollees. Patients treated at the HMO were less likely to receive some care in more than 1 study year.

We can be especially confident of these conclusions because of the experimental design (i.e., a randomized, controlled trial). In addition, we did not observe significant or appreciable differences in the mental health status at enrollment of the groups assigned to the HMO or fee-for-service plans. Further, the differences in use over time remained when we controlled for mental health status at enrollment in the survival analysis. The RAND Health Insurance Study did not include independent diagnostic assessments that would allow us to identify specific clinical subgroups of special policy interest such as the chronically mentally ill. Rather, we used a self-report measure of psychological distress and well-being that is strongly predictive of use of mental health services (14).

Because we observed the same pattern of use for a

group experimentally assigned to an HMO and one that selected the same HMO, we conclude that the higher turnover rate was not due to self-selection of coverage. Our finding that utilization was similar for HMO experimental and control subjects is consistent with the observation of Brady and Krizay (3) that use of mental health services in any particular HMO tends to follow a similar pattern regardless of the benefit structure of the various plans offered by the HMO.

We observed that differences in benefit structure had large effects on utilization for participants in fee-for-service plans. The family pay plan participants had a much lower annual probability of use and a lower probability of use over several years than participants in the HMO or other fee-for-service plans. Of note, the free care plan is more generous than most currently available fee-for-service plans and may be more likely to encourage long-term care than these plans. To the extent that the family pay plans are more comparable to prevailing fee-for-service plans, we would expect to see more people treated at the HMO in any given year or over a several-year period than are treated under fee-for-service coverage.

These conclusions are subject to several limitations. First, we studied only one well-established HMO in one city. Different results may be observed for HMOs in different cities. As noted by Brady and Krizay (3), HMOs vary widely in annual patterns of mental health use; they may also vary in turnover rates. However, many reports of utilization in other HMOs document a reliance on brief treatment (19, 20). High patient turnover may be especially likely in such HMOs.

Second, our results apply when fee-for-service or HMO coverage is assigned to a general population. Although we found similar utilization rates for the control and experimental HMO subjects, we did not study self-selected fee-for-service plans. For example, such plans could have a higher turnover rate because they exclude the uninsured.

Third, our conclusions are limited to the nonelderly, noninstitutionalized civilian population. We also excluded those in the nation's highest income bracket—about 1% of the Seattle area families contacted.

Fourth, the 52-visit limit per person per year effectively excludes long-term intensive psychotherapy. Nevertheless, the RAND Health Insurance Study insurance coverage for outpatient mental health care is more generous than that of most existing plans.

Our results pose an important mental health policy question. Should we support insurance arrangements that encourage more people to eventually receive some care or arrangements that encourage more intensive treatment of fewer people? To address that question requires assessment of the effects of HMO and fee-for-service plans on mental health status (as measured by the Mental Health Inventory) at exit from the experiment. Using data on individuals 14 years old and older at enrollment, Ware et al. (21) reported no significant differences among the plans in mental health status at exit from the study for the average person. However, there were sizable but statistically insignificant adverse effects for those HMO participants with poor initial mental health status. We are currently conducting additional analyses to further explore the effects of HMO and fee-for-service coverage on mental health status.

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Pregnancy-Related Affective Episodes Among Women With Recurrent Depression

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The authors examined 52 women with recurrent depression to determine the differences between women with and without histories of pregnancy-related affective episodes. The women with histories of such episodes (N=24) had been significantly younger at illness onset, were more severely depressed at baseline, and tended to show less emotional stability. The EEG-recorded sleep of the women with pregnancy-related affective episodes was distinguished by longer REM sleep time and more REM activity, differences accounted for almost entirely by the women with histories of only postpartum episodes.

(Am J Psychiatry 1987; 144:288–293)

There is now substantial evidence of an increased incidence of psychiatric disorders during the period of childbearing and lactation. In a study by Paffenbarger et al. (1), the rates for the onset of psychiatric disorder, while relatively low and consistent across the three trimesters of pregnancy, were dramatically higher during the early puerperium, most notably during the first month postpartum. The rates at these times were several times higher than the rate for nonpuerperal women of the same age. Pugh et al. (2) reported similar findings with respect to psychiatric admissions after childbirth; the highest rate was for the early puerperium, and at 9 months postpartum the rate was about the same as for nonchildbearing times. This finding was especially true of admissions for affective illnesses, which were most common during the first 3 months postpartum. Similar findings have also been reported by Seager (3), Sim (4), Jansson (5), Protheroe (6), Brockington et al. (7), and Kendell et al. (8, 9). Finally, the literature on the incidence of mild to moderate depressive episodes among women after childbirth was reviewed by Pitt (10), who reported that it varies depending on the criteria employed but ranges from 3% to 31%.

It was once generally accepted that the period of pregnancy itself is marked by either no change or a lower rate of onset of psychiatric disorder than during postpartum or nonchildbearing times. However, a number of investigators (11–14) have reported depression of at least mild to moderate severity during pregnancy. Although studies examining the relationship of the childbearing period to psychiatric disorder among women have demonstrated higher rates of psychiatric disturbance during this period by means of prospective and retrospective designs, the heterogeneity of the study samples has usually prevented any definite ascertainment of disorder-specific incidence rates.

In a prospective study of 99 women, O'Hara et al. (15) found that the Research Diagnostic Criteria (RDC) (16) for major or minor depression were met by approximately 9% of the women during pregnancy and 12% of the women during the postpartum period. Furthermore, these investigators concluded that the number of previous depressive episodes and the presence of depressive disorder in first-degree relatives were two major "vulnerability" factors in determining who developed a postpartum depressive episode rather than experiencing depressive symptoms.

There is a current trend, particularly among working women, to delay childbearing until later in the reproductive years. It is well established that the overall risk of depressive disorder is greater among women and that it increases with age at least until the fifth decade, so we may be entering a time when more women will approach childbearing already having personal histories of affective disorder (17).

In studying a large group of patients with such histories, we were struck by the fact that almost half of those women who had given birth had each experienced the onset of a depressive episode during pregnancy or in the first several months after delivery. We felt it was important to determine what features might distinguish those women with pregnancy-related epi-

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Supported in part by NIMH grants MH-29618 and MH-30915 and by a grant from the John D. and Catherine T. MacArthur Research Network on the Psychobiology of Depression.

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sodes and to explore whether having a history of such episodes had any impact on the patient's current treatment experience.

METHOD

Subjects

The initial pool from which the subjects for the present study were drawn consisted of the first 119 patients who entered a study on maintenance therapies in recurrent depression. Of these 119, 27 were men and 92 were women. Among the women 52 had given birth to at least one child before entering the study. These women had a mean±SD age of 44.0±10.0 years at the time of their entry into the study and had an average age at onset of illness of 28.8±10.8 years. Although only two previous episodes were required for entry into the study, the mean±SD number was 6.4±3.9. The mean±SD baseline score on the Hamilton Rating Scale for Depression (18) was 23.3±5.0. Thirty-two of the 52 women were categorized as having endogenous depression, and five were diagnosed as bipolar II rather than unipolar.

For the purposes of the present investigation, the subjects were further divided in two ways: 1) according to the presence or absence of any pregnancy-related depressive episode that met the RDC for a major depressive episode and 2) according to the subject's response to acute treatment. Twenty-eight of the 52 women reported no pregnancy-related episodes, while 24 reported one or more episode onsets during pregnancy (N=7), in the first 6 months after delivery (N=11), or both during pregnancy and in the postpartum period (N=6). There was a total of 33 pregnancy-related episode onsets among these 24 women. For seven of the 24 women, the pregnancy-related episode was the first episode (illness onset) of major depression. Of these seven, five women experienced only postpartum episodes and two experienced episodes only during pregnancy. There was no significant difference in the number of pregnancies experienced by the women who had associated depressive episodes (2.4±1.4) and those who did not (2.7±1.1). It did not appear that depressive episodes were more likely to be associated with a first than a subsequent pregnancy. Of the 24 first pregnancies, 15 were associated with episodes of depression, while depressive episodes were experienced in 19 of the 34 subsequent pregnancies (χ^2=0.25, n.s.). Of the 19 women who had more than one pregnancy, 15 had at least one pregnancy without a related depressive episode.

Since one focus of the present investigation was the possible relationship between a history of pregnancy-related depressive episodes and current treatment response, the 52 women were also divided into those who showed a clear remission of symptoms within 8 weeks and remained well for the subsequent 8 weeks ("normal responders"), those who showed a slower and more variable response but nonetheless achieved remission by 16 weeks of acute treatment ("slow responders"), those who showed some response to the treatment regimen but could not be considered fully remitted at 16 weeks ("partial responders"), and those whose response to treatment was so poor that it was deemed necessary to terminate the regimen of imipramine and psychotherapy before the end of 16 weeks and initiate alternative treatment ("treatment terminators"). A computer algorithm was developed for classification of response types. A normal responder was characterized by a Hamilton score of 7 or less by 8 weeks, a score below 10 at 12 weeks, a score of 7 or less at 16 weeks, and at least a 50% reduction in baseline score. A slow responder had either 1) a Hamilton score of 7 or less at 8 weeks, a score of 10 or more at 12 weeks, a score of 7 or less at 16 weeks, and at least a 50% reduction in baseline score or 2) a Hamilton score of 7 or more at 8 weeks and a score of 10 or more at 12 weeks but a score of 8–10 by 16 weeks and at least a 60% reduction in baseline score. All other patients remaining in the study were partial responders.

Study Design

To enter the study on maintenance therapies in recurrent depression, a subject must be between the ages of 21 and 65 years, must be experiencing at least the third episode of unipolar depression, and must have had the immediately preceding episode no more than two and one-half years before the onset of the present episode. A minimum Hamilton depression score of 15 and a minimum score of 7 on the Raskin Severity of Depression Scale (19) are also required. All patients gave their informed consent to participate in this study.

After a 2-week drug-free washout period, each subject is reevaluated with respect to severity of depression and then given a complete initial evaluation including biological (all-night sleep EEG and neuroendocrine studies) and psychosocial (social adjustment, social support, etc.) measures; however, because of the probable influence of acute illness on personality measures, personality features are not evaluated at this time. All subjects then receive the same acute treatment regimen, which consists of imipramine (150–300 mg/day) and interpersonal psychotherapy (20), offered weekly for 12 weeks, then biweekly for 8 weeks, and finally monthly. At whatever point in this acute treatment regimen the patient has maintained a Hamilton score of 7 or less and a Raskin score of 5 or less for 3 weeks, a second biological and psychosocial evaluation is completed. At this evaluation personality is assessed for the first time by means of both self-report and interview measures. The patient then remains in continuation treatment for an additional 17 weeks, during which both Hamilton and Raskin scores and imipramine dose must remain stable. A third evaluation is then conducted, after which the patient is

randomly assigned to one of five maintenance treatments for 3 years or until he or she experiences a recurrence of illness.

Measures

As already noted, the Hamilton Rating Scale for Depression and the Raskin Severity of Depression Scale are employed as both entry and progress criteria. In addition, each patient is assessed at the time of entry into the study with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (21). When a subject has achieved a stable remission, a history of previous depressions, including age at onset, is obtained with the Lifetime History of Affective Disorders interview, developed by us for our studies on recurrent depression. Finally, the present report includes results from the following self-report personality measures and baseline biological measures.

The Hirschfeld-Klerman Personality Battery (22) is a 495-item self-report inventory that encompasses 17 scales drawn from five preexisting personality inventories. The subject is asked to complete the battery over the course of the 3 nights spent in the sleep laboratory.

Cortisol nadir (minimal nocturnal cortisol concentration) is the mean serum cortisol concentration calculated from the lowest three consecutive samples collected during the night. It is expressed in nanograms per 100 ml. Higher values indicate the flattening of the nighttime cortisol rhythm that has been shown to be associated with major depressive disorder (23).

Cortisol latency is the length of time between sleep onset and the rise in cortisol. It is expressed in minutes from sleep onset (minus awake time). Shortened cortisol latency has been found to be a feature of depressive illness (23).

Sleep maintenance represents the proportion of the sleep evaluation period (typically 11:00 p.m. to 6:30 a.m.) after sleep onset that is actually spent asleep. Expressed as a percent, sleep maintenance is typically lower in patients suffering from major depression (24).

REM density is the ratio calculated by dividing the amount of REM activity by the amount of REM time over the course of the night. It reflects the intensity of eye movements during REM sleep and is typically higher in depressed patients (25).

REM latency is the number of minutes between sleep onset and the first REM period. In 1972, Kupfer and Foster (26) identified short REM latency as a marker of depressive illness, and this finding has been replicated in at least 10 other laboratories (24).

The procedures for biological evaluation of patients in the maintenance therapies study have been described in detail elsewhere (27).

Data Analysis

Several types of statistical comparisons were used in this study. Nonparametric data were compared by means of chi-square analyses, while parametric data were compared with t tests, or analyses of variance (ANOVAs) when more than two groups were involved. When appropriate, Neuman-Keuls procedures were used to make post hoc comparisons among groups.

RESULTS

There were no differences between the subjects with histories of pregnancy-related episodes and those without such histories in 1) the rapidity with which they responded to acute treatment, 2) whether they achieved full remission of symptoms and were assigned to the maintenance phase of the study, or 3) whether they experienced a relapse while receiving combined treatment. Furthermore, there were no differences in either speed of response to treatment or likelihood of relapse between the women who had episodes only during pregnancy and those who had them only after giving birth. Differences did emerge, however, when other characteristics were compared.

In table 1 the characteristics of the 28 women with no pregnancy-related episodes are compared with those of the 24 women with such episodes. Although there were no differences in age at entry into the study, duration of the present episode, or number of prior episodes, the women who had experienced pregnancy-related episodes had a significantly higher mean baseline score on the Hamilton scale and had a significantly earlier age at onset of illness.

Both groups of women differed from normal control subjects on five selected scales from the Hirschfeld-Klerman personality battery: emotional stability, objectivity, lack of social self-confidence, orality, and neuroticism (28). Only emotional stability distinguished the two groups (see table 1); the group that experienced pregnancy-related episodes tended to report lower emotional stability. This difference appears to be accounted for entirely by the women who experienced affective episodes during rather than after pregnancy (see table 2). Finally, the baseline EEG sleep characteristics of the two groups are also shown in table 1. There were no differences in sleep maintenance, REM density, REM latency, or cortisol nadir during the night, but the women with pregnancy-related episodes had a significantly longer REM time and more REM activity. These differences appear to be accounted for almost entirely by the 11 women with only postpartum episodes (see table 2).

DISCUSSION

Although, to our knowledge, there have been no previous studies of differences between depressed women with and without histories of pregnancy-related episodes, one might expect to see a number of differences between these two groups of women. Our expectation was that women with histories of such

TABLE 1. Characteristics of Women With Recurrent Depression Who Did Not Have Pregnancy-Related Affective Episodes[a] (N=28) and Those Who Did (N=24)

Characteristic	No Pregnancy-Related Episode Mean	SD	Any Pregnancy-Related Episode[a] Mean	SD	Significance t	df	p
Clinical characteristics							
Age at onset (years)	33.5	11.9	23.2	5.4	4.1	39	.001
Number of prior episodes	6.1	4.0	6.7	3.8	−0.6	50	n.s.
Age at screening (years)	46.0	10.8	41.7	8.8	1.6	50	n.s.
Baseline Hamilton score	21.5	4.6	25.4	4.7	−3.0	50	.01
Duration of current episode (weeks)	19.4	12.2	21.4	15.7	−0.5	49	n.s.
Personality scores							
Emotional stability	15.7	6.3	11.1	7.9	1.9	33	.06
Objectivity	16.5	5.6	16.1	6.7	0.2	32	n.s.
Lack of social self-confidence	34.1	7.7	35.6	9.2	−0.5	33	n.s.
Orality	7.2	3.6	7.3	4.7	−0.1	33	n.s.
Neuroticism	22.4	11.7	28.7	12.9	−1.5	32	n.s.
Sleep characteristics							
Sleep maintenance (%)	90.1	11.8	90.5	8.1	−0.1	50	n.s.
REM time (minutes)	72.8	22.9	87.9	23.5	−2.3	50	.02
REM activity (units)	85.4	34.3	112.0	54.2	−2.1	38	.05
REM density	1.2	0.38	1.3	0.47	−0.6	50	n.s.
REM latency (minutes)	72.5	39.3	70.7	35.2	0.2	50	n.s.
REM activity in first REM period (units)	22.2	14.5	27.6	25.4	−0.9	35	n.s.
Cortisol nadir (ng/ml)	2.3	1.3	2.1	1.7	0.4	35	n.s.

[a]During pregnancy, the first 6 months after delivery, or both.

TABLE 2. Selected Comparisons of Women With Recurrent Depression Who Had No Pregnancy-Related Affective Episodes (N=28) and Those Who Had Episodes During Pregnancy (N=7), the First 6 Months Postpartum (N=11), or Both (N=6)

Characteristic	No Pregnancy-Related Episode Mean	SD	Median	Any Pregnancy-Related Episode: Pregnancy Only Mean	SD	Median	Postpartum Only Mean	SD	Median	During Pregnancy and Postpartum Mean	SD	Median	Comparison of Means (ANOVA) F (df=3)	p
Baseline Hamilton score	21.5	4.6	21.3	24.3	4.5	24.8	25.5	5.1	26.0	26.7	4.8	25.0	3.21	<.03
Age at onset (years)	33.5	11.9	31.5	20.1	4.5	20.3	24.8	4.6	24.7	23.8	6.9	20.5	5.32	<.003
Emotional stability score	15.7	6.3	17.0	6.3	2.4	7.0	15.4	9.2	16.5	7.5	3.2	6.5	3.65	<.02
REM time (minutes)	72.8	22.9	68.5	82.3	21.0	81.0	96.3	26.7	91.0	79.0	17.1	71.0	2.77	<.05
REM activity (units)	85.4	34.3	77.5	86.3	38.4	98.0	137.2	63.9	113.0	95.8	30.2	85.5	4.14	<.01

episodes would be distinguished by 1) a more severe index episode, 2) a more disturbed personality profile, 3) a poorer response to combined acute treatment, and 4) less likelihood of achieving the sustained remission necessary to enter the maintenance phase of the protocol. These expectations were loosely based on an assumption that a history of pregnancy-related episodes would be associated with a greater overall vulnerability, which would be expressed in both greater severity and chronicity. The women with histories of pregnancy-related episodes did enter the study with a significantly higher score on the Hamilton Rating Scale for Depression, and there was a trend for greater pathology on one of the five personality scales; however, the other anticipated differences were not observed. Contrary to our expectations, there were no differences between women with and without histories of pregnancy-related episodes in either the rapidity with which they responded to an acute treatment regimen consisting of imipramine and interpersonal psychotherapy or their likelihood of achieving a sustained remission and entering the study's maintenance phase.

Some differences observed between the patients with and without pregnancy-related episodes were not anticipated. Although the groups did not differ in age at entry into the study or in the number of previous episodes, the women with histories of pregnancy-related episodes had a significantly earlier age at onset of illness. On the average, the women without pregnancy-related episodes had had six episodes in 10 years and the pregnancy group had had approximately six episodes in 20 years, suggesting a different natural course of illness. Perhaps most surprising were the differences between the groups in all-night sleep EEGs: a history of pregnancy-related episodes was associated with significantly longer REM time and more REM activity.

To try to interpret these somewhat unexpected and seemingly unconnected findings, we examined them in relation to the three subgroups *within* the group of patients with pregnancy-related episodes, i.e., those

with episode onsets only during pregnancy, those with onsets only in the postpartum period, and those with onsets both during pregnancy and after childbirth. These analyses revealed that the three subgroups had roughly equal severities of index episodes; however, the early age at onset of illness and the low emotional stability were accounted for primarily by the women with episode onsets only during pregnancy, whereas the differences in REM time and REM activity were accounted for by the women with only postpartum onsets. These findings are somewhat puzzling inasmuch as both the early age at onset and the REM findings could be considered indicative of greater biologic (and perhaps genetic) vulnerability. The lower emotional stability, on the other hand, could indicate vulnerability to psychosocial stressors. Undoubtedly, pregnancy and parturition are both biologic and psychosocial stressors of considerable magnitude. Analyses of larger groups of women with onsets at each of these critical time points might answer these questions.

Since many of these pregnancy-related episodes occurred in the postpartum period, this study highlights the period after childbirth as a period of heightened risk. Finally, two aspects of the longitudinal course of this group of women warrant comment. Akiskal et al. (29) contended that postpartum episodes are predictors of bipolar potential, especially in women under the age of 25 years; however, our data point to the existence of at least a subgroup of women who do not switch from unipolar to bipolar disease. While this sample was selected on the basis of having recurrent nonbipolar disease, it is noteworthy that so many pregnancy-related episodes occurred in young women, including seven pregnancy-related episodes that were the first episodes of depression. Second, a recent follow-up study (30) demonstrated that the probability of a recurrent affective (unipolar) course after a postpartum episode was 43%. Examining this issue from the other side of the coin, we find that among women with a documented recurrent affective disorder, 71% of those with any pregnancy-related episode had at least one episode of postpartum depression, and 33% of the women who had children had at least one episode of postpartum depression.

These suggestive findings of differences among the three subgroups of women with pregnancy-related episodes point to the need to reexamine these variables in a larger sample of women. For example, what are the differences between women who each have a single pregnancy-related episode and those with multiple episodes? Also unexplored at this point are the possible differences among these women with respect to family history and the effect of a history of pregnancy-related episodes on the outcome of maintenance treatment. Finally, these groups of individuals with pregnancy-related episodes should be compared to women with recurrent depression who have not had children to determine their differences on a variety of clinical, biological, and personality measures.

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First-Rank Symptoms as a Diagnostic Clue to Multiple Personality Disorder

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Thirty patients with multiple personality disorder had one or more of Schneider's 11 first-rank symptoms at initial assessment (mean = 3.6; range=1–8). The author describes these symptom categories, eight of which were noted in the patients he interviewed, and illustrates them from the patients' case material. He suggests that inquiry about first-rank symptom phenomena may be a valuable diagnostic clue to the presence of multiple personality disorder.

(Am J Psychiatry 1987; 144:293–298)

In 1939 Schneider described certain symptoms as pathognomonic of schizophrenia:

> Audible thoughts; voices heard arguing; voices heard commenting on one's actions; the experience of influences playing on the body (somatic passivity experiences); thought-withdrawal and other interferences with thought; diffusion of thought; delusional perception and all feelings, impulses (drives), and volitional acts that are experienced by the patient as the work or influence of others. When any of these modes of experience is undeniably present and no basic somatic illness can be found, we may make the decisive clinical diagnosis of schizophrenia. (1, pp. 133–134)

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These pathognomonic findings, called first-rank symptoms, were neither necessary for the diagnosis nor continuously present. However, if present, they "have a decisive weight beyond all other . . . and must have undisputed precedence when it comes to the allocation of the individual case" (1, p. 135).

Chandrasena (2) observed that Schneider's assertions remained unchallenged until the 1970s. However, in 1973, Carpenter et al. (3) reported that although 51% of their schizophrenic cohort endorsed first-rank symptoms, so did 23% of the affective psychosis group and 9% of the neurosis and character disorder groups. Taylor and Abrams (4, 5) found first-rank symptoms in 12% and 8% of two groups of manic patients. Wing and Nixon (6) found first-rank symptoms in 13% of patients with mania, 4% of those with depressive disorders, and 2% of those with neuroses. Koehler and Seminario noted first-rank symptoms in about 15% of a group of patients with affective disorders (7) and observed that 27.7% of a group of "Schneider-positive schizophrenics" satisfied criteria for schizoaffective disorder (8). Gharagozlou and Behin (9) discovered first-rank symptoms in depressive, manic, paranoid, neurotic, and character disorder patients and in 2% of their normal subjects.

At present, it is generally accepted that first-rank symptoms are not pathognomonic for schizophrenia (10). However, concern has been expressed that first-rank symptoms have been operationalized improperly, leading to false-positive endorsements by those unfamiliar with Schneider's actual observations. Unfortunately, Schneider did not describe the symptoms precisely; most were simply listed. They have been defined and elicited differently by several researchers. Hoenig (11) has criticized both Mellor's operationalizations

(12) and the questions from a structured interview (13) used by Carpenter et al. (3) as being capable of eliciting positive answers that have "nothing to do with Schneider's FRSs [first-rank symptoms]" (11, p. 84). Schneider's student Koehler (14) concluded that differences in the interpretations and boundaries of clinical phenomena might explain discrepant findings. Andreasen and Akiskal (15) noted "the possibility that those without extensive training in the phenomenologic approach may overendorse their (FRSs) presence, thereby diluting the specificity of the test."

Despite psychiatrists' interest in first-rank symptoms, few have attempted to explain them. Recently, Nasrallah (16) proposed that normal interhemispheric integration necessitates "the inhibition of any awareness by the verbally expressive hemispheric consciousness (usually the left) that it actually receives and sends thoughts, intentions, and feelings from and to another (right hemispheric) consciousness" (p. 273). A disinhibition may lead to the left hemisphere's awareness of its "being 'influenced' by an unknown 'external force' which is in fact the right hemisphere" (p. 273), resulting in several of the Schneiderian first-rank symptoms.

In 1974, shortly after the publication of Mellor's descriptors (12) and the first-rank-symptom-oriented questions in structured interview instruments (3, 13), I noted phenomena suggestive of first-rank symptoms in several patients with classical multiple personality disorder, which stimulated further explorations.

METHOD

Beginning in 1975, I inquired about first-rank symptoms in my first interview with each patient referred to me for consideration or confirmation of the diagnosis of multiple personality disorder. I used Mellor's first-rank symptom definitions (12) and generally employed the interview questions listed by Carpenter et al. (3). However, I separated "made" feelings from "made" influences, following Mellor rather than Carpenter et al. I expanded somatic passivity inquiries, thinking that the items cited by Carpenter et al. were limited and suggestive. I evolved novel questions for voices arguing and voices commenting because these items often proved unscorable (3). Also, I elected to pursue delusional percept in ways unique to each patient, because simple inquiry did not appear to yield scorable answers (3). First-rank symptoms elicited at first contact were enumerated; others, observed later, were not. Items were scored as present or absent.

Many patients in the study were given a diagnosis before the appearance of *DSM-III*, but all satisfied its criteria, as well as the amnesia criterion of Coons (17) and the repeated observation criterion of Braun (18). To reduce the possibility of the inadvertent inclusion of patients misdiagnosed as having multiple personality disorder but suffering from other conditions, the study population was restricted further to patients who had achieved fusion of personalities according to research criteria (19) and maintained it on reassessment 27 months or more after apparent fusion (20, 21). Patients who required neuroleptics, antidepressants, lithium, or anticonvulsants were excluded.

In sum, of 241 multiple personality disorder patients interviewed (197 of them were women), 135 were excluded because they had not achieved fusion. Of 106 who did achieve fusion, 54 were excluded because at follow-up they fell short of study requirements (20, 21). Of the remaining 52, reported elsewhere (21), 11 were excluded because of relapse phenomena, three for falling short of strict inclusion criteria, four for requiring medications for coexisting seizure and/or affective disorders, and four because they were assessed before the formalization of the first-rank symptom inquiry protocol. This left 30 patients in the study group, nine men and 21 women.

RESULTS

Observations

All study patients reported at least one first-rank symptom. Thirty patients endorsed a total of 108 first-rank symptoms, ranging from 1 to 8 and averaging 3.6. Eight of the 11 first-rank symptoms were acknowledged; the prevalence of each is indicated in table 1. Each symptom was reported by a much larger percentage of patients as their treatments proceeded.

Illustrations

Mellor's (12) descriptions of Schneider's 11 first-rank symptoms are given below, followed by illustrations from the patients studied and discussion.

1. *Audible thoughts.* "The patient experiences auditory hallucinations, with voices speaking his thoughts aloud" (12, p. 15). Sometimes opposite or contradictory notions are heard. Mellor noted that Kraepelin felt that such hallucinations could either follow the thought or precede it. In the latter case, the hallucinated voice is experienced as one's own thought.

No patients in this study endorsed such experiences initially. However, during therapy, several had personalities that, in trying to deny and disavow their multiple personality disorder, heard another alter's hallucinated voice and immediately defined what it said as their own thoughts.

2. *Voices arguing.* "There are two or more hallucinatory voices in disagreement, or in discussion. The subject is usually the patient, who is referred to in the third person" (12, p. 16).

Many presenting personalities had overheard others in conversations. Often a patient described two or more voices discussing how to help or harm him or overheard a punitive personality who wished to hurt or sabotage him arguing with a protector personality who opposed such action.

TABLE 1. Schneider's First-Rank Symptoms in 30 Patients With Multiple Personality Disorder

Patient Number	Number of Personalities	First-Rank Symptom Number[a]											Number of Symptoms Endorsed by Patient
		1	2	3	4	5	6	7	8	9	10	11	
1	2				+				+				2
2	86		+			+			+	+			4
3	3		+				+		+	+	+		5
4	5					+			+				2
5	25		+	+	+	+	+		+	+	+		8
6	3										+		1
7	9		+						+				2
8	5		+						+	+	+		4
9	2								+				1
10	3			+					+		+		3
11	18				+		+		+	+			4
12	2								+	+	+		3
13	3					+	+						2
14	5					+			+	+	+		4
15	12		+	+			+		+				4
16	28				+		+			+			3
17	2								+	+			2
18	8				+		+		+	+			4
19	5				+					+	+		3
20	33		+		+	+	+		+	+			6
21	5				+								1
22	5		+	+		+	+		+		+		6
23	5		+	+	+	+	+		+	+	+		8
24	5						+		+				2
25	88		+	+		+	+				+		5
26	22			+	+	+	+		+		+		6
27	16					+			+		+		3
28	5			+		+				+			3
29	6			+		+			+				3
30	8				+	+				+	+		4
Total	424	0	10	9	11	14	13	0	23	14	14	0	108
Patients with the symptom (%)	14.1[b]	0	33.3	30	36.7	46.7	43.3	0	76.7	46.7	46.7	0	3.6[c]

[a]The 11 symptoms are described in text.
[b]Average number of personalities per patient.
[c]Average number of first-rank symptoms per patient.

3. *Voices commenting on one's action.* "The content of the auditory hallucination is a description of the patient's activities as they occur" (12, p. 16).

Often the comments included brutal deprecation, as is found in psychotic depression. One patient heard a voice that commented on my interview with her: "She is trying to tell him what is going on inside her, but she can't. She stumbles over her words because she is sure she can't say it right, she can't make him believe her. She is failing. She always fails. Now she begins to cry." A critical alter was mocking the presenting personality's efforts to explain her plight.

4. *Influences playing on the body (somatic passivity).* "The patient is a passive and invariably reluctant recipient of bodily sensations imposed upon him by some external agency" (12, p. 16). These are experienced both as bodily change and as externally controlled: a single experience rather than a delusional interpretation of an abnormal bodily sensation.

One woman said, "It's like someone is shoving something up my anus, tearing me apart. It goes all over my stomach. I can't sit down because of this." This proved to be a somatic memory of a forceful anal penetration by her father, who violated one daughter in the presence of the others. Three siblings confirmed witnessing such violations.

5. *Thought withdrawal.* "The patient describes his thoughts being taken from his mind. As his thoughts cease, he simultaneously experiences them being withdrawn by some external force" (12, p. 16).

Typically, patients would experience this as an imposed blankness or emptiness of mind in connection with discussing an area that—whether it was then known to be upsetting or not—later proved to be stressful. Often other personalities were found to have blocked the access of the personality being interviewed to particular material. One patient, when asked about her deceased mother, replied: "She was a good woman. . . . Doctor, I'm sorry, it's like something just took the thoughts out of my mind. What were we talking about?" Her mother, in fact, had abused her severely and described these activities in her diary, which was discovered later.

6. *Thoughts ascribed to others (thought insertion).* "The patient experiences thoughts which have not the quality of being his own" (12, p. 17). Some external

agency is felt to have imposed the thoughts upon the patient's mind.

One patient was plagued with the thought of hitting me, a thought he found repugnant and not his own. Later, he learned that these were the thoughts of another alter, who opposed being discovered. As barriers were lowered, he was increasingly aware of these thoughts and understood their origin.

7. *Diffusion or broadcasting of thoughts.* "The patient, during the process of thinking, has the experience that his thoughts are not contained within his own mind. The thoughts escape from the confines of the self into the external world, where they may be experienced by all around. There is usually a secondary delusional explanation of this phenomenon which may invoke the use of telepathy, television, etc." (12, p. 17).

No patients endorsed this initially. Later, many revealed the suspicion that a parent or I could read their minds, but none had a firm global sense that all could experience their thoughts.

8. *"Made" feelings.* "The patient experiences feelings which do not seem to be his own. The feelings are attributed to some external source and are imposed upon him" (12, p. 17).

Usually, such experiences reflected one alter's experiencing another's feelings. Less frequently, this was traced to the incipient eruption of a repressed affect-laden experience. Many patients initially experienced apprehension in the interview, found themselves crying, or sensed a panicky need to leave the room, yet they did not have a sense of owning the feeling, despite experiencing it intensely. Sometimes other alters tried to influence the one being interviewed by imposing feelings. One such alter later said, "I wanted her to feel so scared she'd run out. I was scared and wanted to leave, but I couldn't take over and run away."

9. *"Made" impulses (drives).* "A powerful impulse overcomes the patient to which he almost invariably gives way. The impulse to carry out this action is not felt to be his own, but the actual performance of the act is" (12, p. 17).

Unlike the obsessive-compulsive patient, who perceives the drive as alien but emanating from within himself, these patients experienced impulses as made by some external agency and imposed from without. Many described fighting and then giving in to impulses to harm themselves or behave inappropriately. Later in treatment, it was understood that alters behind the scenes, without assuming full executive control, nonetheless had imposed their will. Often prolonged battles occurred before impulses were acted upon or quashed.

10. *"Made" volitional acts.* "The patient experiences his actions as being completely under the control of an external influence. The movements are initiated and directed throughout by the controlling influence, and the patient feels he is an automaton, the passive observer of his own actions" (12, p. 17).

Often an alter takes over control without the alter that has been superseded losing a sense of consciousness or presence. Hence, the replaced alter becomes the hapless observer of activities that may repel it. A patient described episodes of promiscuity; she was aware that her body was speaking and acting seductively and engaging in undiscriminating and uninhibited sexual activity. The voice she heard was not experienced as hers; the behaviors were experienced as imposed upon her. She was experiencing another alter's activities.

11. *Delusional perception.* This is "a two stage phenomenon. The delusion arises from a perception which to the patient possesses all the properties of a normal perception, and which he acknowledges would be regarded as such by anyone else. This perception however has a private meaning for him, and the second stage, which is the development of the delusion, follows almost immediately. The crystallization of an elaborate delusional system following upon the percept is often very sudden" (12, p. 18).

No patients in this series endorsed this experience. However, patients with both multiple personality disorder and bipolar affective disorder have shown such phenomena. Some multiple personality disorder patients, after considerable introspection and frustration in efforts to understand themselves, describe analogous phenomena. However, the time course of their evolution is usually quite gradual, and the delusions or pseudodelusions usually diminish and resolve with insight alone.

DISCUSSION

First-rank symptoms can be documented in multiple personality disorder patients. Recent reviews (10, 15) suggest that first-rank symptoms occur in about half of all schizophrenic patients. These symptoms are noted in organicity (1) and in many nonpsychotic conditions (3, 6, 9) and are found in individuals with no diagnosable mental disorder (9). Their presence is not indicative of any particular condition. Despite the fact that the criteria for this study were selected before the appearance of publications cautioning against overendorsement or misendorsement of first-rank symptoms (13–15)—and thus it is possible that some symptoms which Schneider-trained observers would not have accepted were scored as present—it is clear that a high percentage of multiple personality disorder patients endorse first-rank symptoms. It is reasonable to infer that some multiple personality disorder patients with these symptoms have been given an erroneous diagnosis of schizophrenia.

Elsewhere I have noted that first-rank symptoms and many symptoms usually associated with psychosis are common in multiple personality disorder (19, 22–25). Bliss (26) found that 64% of his multiple personality disorder patients had symptoms associated with schizophrenia. Of them, 64% heard voices, 36% saw visions, 73% felt that someone was trying to influence their minds, and 55% felt that someone was control-

ling their minds. Twenty-seven percent demonstrated thought broadcasting, a symptom not endorsed in this series. He also noted that 64% experienced mind blocking, and 82% felt their minds were stopping. Coons and Milstein (27) found auditory hallucinations in 60% and visual hallucinations in 20% of their multiple personality disorder patients. Putnam et al. (28) found that 30% of their multiple personality disorder patients had auditory hallucinations, 28% had visual hallucinations, 21% apparent delusions, and 19% apparent thought disorder. Forty-nine percent had been given a previous diagnosis of schizophrenia. While findings in these series and in the current study are difficult to compare, taken as a whole they constitute a forceful argument that the findings in multiple personality disorder may overlap with and/or mimic those of schizophrenia, psychotic depression, and schizoaffective disorder, leading to misdiagnosis. Rosenbaum (29) offered related arguments.

Findings suggestive of first-rank symptoms should prompt the inclusion of multiple personality disorder in the differential diagnosis. Multiple personality disorder often proves difficult to diagnose; Putnam et al. (28) found that their 100 patients averaged 6.8 years between their first mental health assessments for symptoms referable to multiple personality disorder and their accurate diagnosis, during which time they had an average of 3.6 misdiagnoses. Furthermore, many multiple personality disorder patients try to evade detection (24) yet do not realize that endorsement of a first-rank symptom may be a diagnostic clue.

This study's findings do not allow the conclusion that all multiple personality disorder patients will endorse first-rank symptoms during their initial assessment or that the reported number of symptoms per patient is representative of all multiple personality disorder patients. The selection criteria perforce overrepresent cooperative and successful patients. I have seen several multiple personality disorder patients disavow first-rank symptoms initially but acknowledge them later in treatment.

It is noteworthy that the reporting and/or acknowledgment of first-rank symptoms increases as treatment proceeds. Perhaps, as patients' trust in their therapists increases and the therapeutic alliance becomes stronger, they feel more free to acknowledge these symptoms. Many patients spontaneously say that they initially feared to reveal them, lest they confess to being "out of control" or "crazy." Also, as treatment continues, more experiences are recalled and/or become accessible to reporting, and therapy, by breaching the defensive dissociative barriers, gradually weakens the obstacles that inhibit each personality's perception of the experiences, feelings, and behaviors of the others and thereby facilitates first-rank symptom experiences. This is consistent with clinical experience. Furthermore, patients' experiences of first-rank symptoms are expressions of their personalities' patterns of interaction at a given point in time. To the extent that alters communicate and try to influence one another short of taking over completely, the likelihood of first-rank symptom experiences is increased.

It is now clear that personalities can act and influence behavior even when they do not have complete or observable executive control (22, 24). A multiple personality disorder patient may be influenced indirectly by personalities that do not assume total dominance; in fact, in some patients with undisputed classic multiple personality disorder, this may be their characteristic adaptation for long periods of time (24). This "new" observation is simply a rediscovery of venerable findings. Ellenberger's comprehensive study (30) demonstrated that contemporary multiple personality disorder is the secularized descendant of the Judeo-Christian possession syndrome. The possession syndrome had two variants, both characterized by the presence of separate entities in contention for control. In somnambulistic possession, when one entity took over control of the body from another the displaced entity was amnesic for that period of time. In lucid possession, however, one or more entities struggled for control of the body, each aware of the other(s) or at least aware that some attempt was being made to deprive it of control. In given cases the nature of each of these entities and the degree of its awareness of the other—and their awareness of the nature and process of their struggle—might assume both forms and change over time (30). Such fluctuations are also consistent with the natural history of multiple personality disorder (24). The clinical relevance of this historical note is that when the presenting personality is unaware of the existence or behaviors of the other personalities, and/or when the alternation of the personalities is too infrequent or too well hidden to be noted during a routine clinical assessment, endorsement of first-rank symptoms may suggest unsuspected multiple personality disorder.

Another connection between first-rank symptoms and multiple personality disorder is suggested by the observation that multiple personality disorder patients are a highly hypnotizable group of patients in both clinical (19, 31) and research (32, and unpublished data of Lipman, Frischholz, and Braun) settings and the observation that most first-rank symptoms resemble phenomena commonly encountered in hypnosis. Bliss (32) described multiple personality disorder as a "hypnotic pathology." Hallucinations may be experienced by hypnosis subjects, either spontaneously, in the course of certain procedures, or in response to suggestions. The experience that phenomena are happening to one without one's volition is intrinsic to hypnotic suggestion (33, 34). It is arguable that the personalities' internal hypnotic/autohypnotic experiences may induce the first-rank passive-influence experiences and characteristic hallucinations so frequently experienced by multiple personality disorder patients. Indeed, it is a clinical commonplace for personalities to state that they have made another see or hear something, influenced another's perceptions, caused a sensation, impulse, or action in some other alter, or taken

away the alter's memory. Overlaps among first-rank symptoms, hypnotic phenomena, and the manifestations of multiple personality disorder are numerous and thought provoking.

Although the prevalence of first-rank symptoms in multiple personality disorder populations before treatment is unknown and the findings of this study must be regarded as preliminary, it appears that the endorsement of first-rank symptoms in a patient's initial assessment should alert the clinician to include multiple personality disorder in the differential diagnosis. First-rank-symptom-oriented inquiries may be particularly useful when special circumstances (such as forensic assessment) warrant excluding inquiries that, in their very asking, might suggest symptoms commonly associated with multiple personality disorder.

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Auditory Hallucinations in Combat-Related Chronic Posttraumatic Stress Disorder

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Intrusive images have been reported to occur in a broad range of people with posttraumatic stress disorder, but the frequency of intrusive auditory perceptions has rarely been addressed. This study compared five posttraumatic stress disorder veterans experiencing auditory hallucinations with 31 nonhallucinating veterans on demographic, military, postmilitary, and symptom variables. Veterans who reported auditory hallucinations had higher combat exposure and more intense posttraumatic stress disorder symptoms than the other veterans. These veterans also tended to be more refractory to treatment than veterans with no hallucinations. Clinical vignettes of the veterans with auditory hallucinations are given, and the implications of the results for a subgroup of chronic posttraumatic stress disorder veterans are discussed.

(Am J Psychiatry 1987; 144:299–302)

The most prominent clinical features of posttraumatic stress disorder, according to *DSM-III*, include reexperiencing the trauma, numbed responsiveness or reduced involvement with the external world, and a variety of other depressive, autonomic, and cognitive symptoms. These symptoms may be present in varying degrees in posttraumatic stress disorder patients, but reexperiencing the traumatic event is a core characteristic that often takes the form of recurrent unpleasant images, nightmares, and symptom triggering in situations similar to the event (1, 2). Although clinical reports have documented intrusive visual, affective, and somatic reexperiences in posttraumatic stress disorder combat veterans (3, 4), little attention has been given to the assessment of analogous auditory perceptions in this population. Similarly, war veterans with dissociated states, hypnagogic hallucinations, and pseudo and real visual hallucinations have been described (5, 6), but auditory hallucinations have rarely been discussed in the literature.

Van Putten and Emory (6) described two cases of "traumatic neuroses" in Vietnam veterans who experienced auditory hallucinations. In one case the patient reported hearing enemy footsteps and voices telling him to commit suicide, and in the other the patient heard the groaning of wounded men calling for help. However, both of these veterans also exhibited explosive rages in altered states of consciousness, which is not a *DSM-III* criterion for posttraumatic stress disorder and is suggestive of a psychotic process secondary to the traumatic event. The present article focuses on auditory hallucinations in combat veterans with posttraumatic stress disorder who showed no other psychotic symptoms.

METHOD

The subjects were 36 male psychiatric inpatients at the West Los Angeles Veterans Administration Medical Center who were referred for diagnostic assessment and (when appropriate) treatment of posttraumatic stress disorder over a 1-year period. All patients met *DSM-III* criteria for posttraumatic stress disorder as well as more stringent criteria based on a structured interview and the Minnesota Multiphasic Personality Inventory (7, 8). This interview provided information regarding patients' demographic characteristics, their military and postmilitary functioning, and the severity of a wide range of psychiatric symptoms. In five of the 36 cases, clinical interviews revealed the presence of auditory hallucinations. All of the veterans with positive diagnoses of posttraumatic stress disorder had experienced moderate to high levels of war trauma assessed by the Combat Exposure Scale (9), and none had been on active military duty in at least 10 years. Each veteran with posttraumatic stress disorder and auditory hallucinations had received extensive chemotherapy with various neuroleptics, but in no case did the medication ameliorate the hallucinations. Thirteen of the 36 veterans with positive diagnoses of posttraumatic stress disorder were engaged in imaginal flooding treatment (10).

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Supported in part by NIMH grant MH-39998.

The authors thank David W. Foy, Ph.D., and Pete Donohoe, Ph.D., for their help in conducting this study.

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TABLE 1. Symptom Self-Ratings in Veterans With Posttraumatic Stress Disorder Who Had (N=5) or Did Not Have (N=31) Auditory Hallucinations

Symptom	Self-Rating (0=no problem, 4=extreme problem)				Student's Two-Tailed t Test		
	Auditory Hallucinations		No Auditory Hallucinations				
	Mean	SD	Mean	SD	t	df	p
No leisure activities	3.4	0.5	1.5	1.4	2.92	34	.006
Difficulty concentrating	3.4	0.9	1.8	1.2	2.71	34	.011
Difficulty with memory	3.4	0.9	1.9	1.2	2.53	34	.016
Excessive jumpiness	3.6	0.5	1.8	1.4	2.64	34	.012
Waking during the night	3.4	0.9	1.8	1.4	2.30	33	.028
Avoidance of activities that remind you of unpleasant events	3.6	0.9	2.0	1.4	2.33	34	.026
Panic attacks	2.8	1.3	1.3	1.4	2.20	34	.035
Heart palpitations or racing	2.2	1.8	0.9	1.1	2.22	34	.033
Trouble trusting others	3.6	0.5	2.6	1.2	1.80	34	n.s.
Difficulty falling asleep	2.6	1.6	2.7	1.2	0.11	33	n.s.
Easily fatigued	2.8	1.1	2.0	1.3	1.30	34	n.s.
Tension and anxiety	2.8	1.6	2.6	1.0	0.34	34	n.s.
Suicidal thoughts	2.2	1.8	1.5	1.5	0.89	34	n.s.
Depression	3.4	0.9	2.5	1.2	1.36	34	n.s.
Early morning awakening	2.8	1.8	2.0	1.6	1.00	34	n.s.
Loss of interest in usual activities	2.8	1.6	2.1	1.4	1.07	34	n.s.
Abusive drinking	1.8	2.0	1.8	1.6	0.00	34	n.s.
Restlessness	3.4	0.9	2.9	0.9	1.10	34	n.s.
Nightmares	3.2	0.8	2.5	1.2	1.13	34	n.s.
Irritability	2.6	1.7	2.1	1.1	0.80	34	n.s.
Pervasive disgust	2.4	1.5	2.1	1.1	0.48	34	n.s.
Hostility/violence	2.4	1.1	1.5	1.2	1.47	34	n.s.
Marital problems	0.8	1.3	1.3	1.7	0.70	34	n.s.
Inability to express feelings	2.8	1.6	2.0	1.3	0.63	34	n.s.
Feeling emotionally numb	2.6	1.7	2.1	1.3	0.80	34	n.s.
Vivid memories of prior unpleasant events	3.6	0.5	2.8	1.3	1.33	34	n.s.

RESULTS

Posttraumatic stress disorder veterans experiencing auditory hallucinations were compared with nonhallucinating veterans on the variables obtained in the structured interview, which included demographics, military-related variables, postmilitary adjustment, and symptoms. A chi-square test performed on race and the presence of auditory hallucinations was significant, $\chi^2=8.03$, df=2, $p<.03$, indicating that more veterans with hallucinations than without were Hispanic (total racial composition: white, N=20; black, N=10; Hispanic, N=6). The two groups did not differ ($p>.10$) in any other of the demographic variables, including age (mean±SD=38.8±8.1 years), years of school (mean±SD=11.4±1.6 years), and marital status (single, N=9; married, N=11; divorced, N=16). There were no significant differences between the two groups for the following military-related variables: the war in which they fought (World War II, N=1; Korean, N=4; Vietnam, N=31), whether they enlisted (N=27) or were drafted (N=9), their age at induction (mean±SD=18.8±2.4 years), number of months in service (mean±SD=14.4±6.8 months), whether or not disciplinary action was taken against them (yes, N=16; no, N=20), and alcohol or drug abuse. However, veterans with auditory hallucinations (mean=6.1, range=0–7) had significantly more combat exposure than nonhallucinating veterans (mean=4.9) (t=2.19, df=32, p=.036). The postmilitary variables examined were social support, number of psychiatric hospitalizations, number of arrests, and the extent to which the patient had talked about the war since his discharge from the military. The two groups did not differ in any of these variables ($p>.05$).

Symptom ratings were obtained by having patients rate the degree of problem experienced on a 5-point Likert-type scale (0=no problem, 4=extreme problem). The mean symptom ratings for the two groups and the probability levels are in table 1. Inspection of this table shows that the auditory hallucination group of posttraumatic stress disorder veterans had higher symptom scores on 23 of the 26 symptoms and that this difference was statistically significant ($p<.05$) for eight of these symptoms.

Evaluation of response to imaginal flooding treatment was conducted by assigning treated patients to one of four categories: veteran terminated treatment, no response (less than 20% reduction in posttraumatic stress disorder symptoms), partial response (between 20% and 80%), or response (greater than 80%). Of the four patients with auditory hallucinations who underwent imaginal flooding treatment, two did not respond and two responded partially; the fifth hallucinating patient left the hospital before treatment could be initiated. In comparison, of the nine treated patients without hallucinations, three terminated treatment prematurely, one failed to respond, two re-

sponded partially, and three responded completely. Only 13 veterans were treated with imaginal flooding, but the results suggested a trend for veterans with auditory hallucinations to be less responsive. This group was also less likely than veterans who did not experience hallucinations to terminate treatment prematurely.

CASE REPORTS

Case 1. Mr. A, a 50-year-old Hispanic veteran, had fought for 13 months in the Korean War when he was 16 years old. During the war he had fought with ground troops, engaged in hand-to-hand combat, killed enemy soldiers, and witnessed the deaths of several close friends. His chief complaints were auditory hallucinations, nightmares, and depression. Mr. A heard voices inside his head of people he believed he had killed in Korea and of some recently deceased relatives. He reported that the voices cried to him and criticized him, at times encouraging him to take his life. The patient stated that he had been hearing these voices for many years, starting several years after he had returned from Korea. Nonetheless, he had been able to work fairly consistently as an engineer since his discharge from the army.

Mr. A received several months of intensive imaginal flooding treatment (10), which was successful in alleviating his auditory hallucinations as well as his other posttraumatic symptoms. A year and a half later, following the deaths of several close family members, the veteran experienced a return of his posttraumatic stress disorder symptoms, including his auditory hallucinations. He returned to the hospital for further treatment.

Case 2. Mr. B, a 55-year-old Hispanic veteran, had fought for 6 months in the Korean War when he was 18 years old. He was hospitalized with complaints of intense guilt, suicidal ideation, auditory hallucinations, nightmares, and depression, in addition to classical posttraumatic stress disorder symptoms. Although the veteran had had considerable combat experience, including multiple shrapnel wounds, which terminated his tour of duty, his auditory hallucinations and other symptoms focused on one specific event: shooting a young North Korean soldier who was wounded. Auditory hallucinations involving a voice, ascribed to the Korean, that berated the patient and told him to commit suicide began about 1 week later and had continued ever since. The voice was perceived as coming from the patient's environment, not within his head. Mr. B sought psychiatric treatment while still in the service but owing to negative experiences left the hospital. Although his hallucinations and other symptoms did not decrease, he managed to work steadily and raise a family. Approximately 3 months prior to his current hospitalization, the symptoms unexplainably worsened; following a near suicide attempt on a freeway, he sought professional help.

Mr. B's symptoms proved extremely refractory to a variety of treatment modalities, including numerous psychotropic medications. He agreed to a trial of imaginal flooding treatment and was placed on one-to-one, 24-hour supervision as a suicide precaution. The veteran received four flooding sessions, after which he attempted suicide, and treatment was suspended. The patient continued to be followed for maintenance; however, his symptoms remained under tenuous control.

Case 3. Mr. C, a 37-year-old black veteran who had served 11 months in Vietnam, was admitted to the hospital with symptoms including insomnia, nightmares, frequent bursts of anger, nervousness, and headaches. In Vietnam he had served as a supply truck driver, where on several occasions his convoy was attacked and some men were seriously wounded. The veteran also reported being deeply disturbed by the loss of a close friend who had been killed in combat.

Mr. C reported being very distressed by voices, which he heard through his ears, of his friend who had died and of some of his comrades who were wounded in one of the attacks. The voice of his friend sometimes merely spoke to him; at other times it told him to kill himself. The voices of the wounded men were heard as groans and cries, similar to those he heard on the night they had been attacked. The veteran had worked in a variety of odd jobs since his discharge from the service, but in the past year he had been homeless and unable to work.

Six flooding treatment sessions were conducted. Initially he showed a favorable response to the treatment and his mood improved. However, his improvement then reversed, and many of his symptoms returned to their baseline level. Although the patient continued to report auditory hallucinations, he said that his feelings about his friend who had died had changed and he was now able to view their relationship in a positive light.

Case 4. Mr. D, a 52-year-old white Korean War veteran, had had numerous previous hospitalizations for alcohol abuse and posttraumatic stress disorder. He had entered the service at age 18 and served in Korea for 28 months. Combat exposure was quite extensive; Mr. D had received numerous battle citations and had been taken prisoner of war by the North Koreans. He was admitted to the hospital with complaints of intense guilt over the many soldiers he had killed, depression, suicidal ideation, classic posttraumatic stress disorder symptoms, and auditory hallucinations. The patient reported hearing voices that emanated both from within his head and from the outside. The voices were perceived as being those of his fellow soldiers, who told him to kill himself and that it was time to join those he had killed. He claimed that the voices were present even after successful periods of detoxification for alcohol dependence. Mr. D left the hospital against medical advice prior to the instigation of behavioral treatment for posttraumatic stress disorder.

Case 5. Mr. E, a 35-year-old Hispanic veteran who had served in the Vietnam War for 18 months, was admitted to the hospital complaining of depression, alienation, and auditory hallucinations. In Vietnam he had served as a "point man," drawing enemy fire and frequently engaging in combat. He had seen several close friends be killed and had personally been responsible for the deaths of enemy military personnel and the accidental deaths of enemy civilians. On one occasion he became enraged at a commanding officer who had egged him into combat, and he impulsively killed a prisoner of war whom he had just captured. Mr. E's auditory hallucinations, heard through his ears, included voices of people he had killed, crying of a distressed comrade, laughter, mortar and gunfire, and sounds of helicopters and airplanes. The veteran also reported occasional visual and olfactory hallucinations that were usually related to deaths he had witnessed in combat. Since his discharge he had worked irregularly in the construction business, but despite his competence and success he felt no satisfaction and was often disturbed by his memories of Vietnam.

Mr. E received 17 imaginal flooding treatment sessions. Although he reported that he found the treatment sessions helpful, his self-reported symptoms indicated a steady worsening in posttraumatic stress disorder symptoms. Treatment was terminated when his repeated challenges to his inpatient treatment team made him a management problem on the ward, and he was discharged from the hospital.

DISCUSSION

While rarely discussed in the literature, our experience suggests that persistent auditory hallucinations can accompany posttraumatic stress disorder in the absence of any gross impairment in reality testing or other psychotic symptoms. The hallucinations are typically depressive in nature, and in four of the five cases they directed the patient to commit suicide. In the case of Mr. B, these hallucinations carried an elevated risk for suicide.

Whether the presence of auditory hallucinations in posttraumatic stress disorder indicates a variant of the disorder worthy of differentiation is unknown at this time. Although our sample is small, the data do suggest that significant differences characterize posttraumatic stress disorder patients with auditory hallucinations. A significantly greater proportion of veterans with auditory hallucinations (60%) than without hallucinations (10%) were Hispanic, suggesting that cultural factors may play a role in the development of this symptom. However, these two groups differed in other symptoms as well. Specifically, patients with hallucinations, when compared with other posttraumatic stress disorder patients, were more likely to complain of greater severity for symptoms that appear to cluster around physiological arousal (jumpiness, avoidance of activities that arouse unpleasant memories, panic attacks, heart racing, waking during the night) and cognitive dysfunction (memory and concentration difficulties). In other respects, the patients with auditory hallucinations were quite similar to the other posttraumatic stress disorder patients. This suggests that chronic posttraumatic stress with auditory hallucinations may be a posttraumatic stress disorder subtype that is not a function of substance abuse or psychotic depression. It is possible that these patients have a constitutional increased sensitivity to the development of auditory hallucinations. This might account, in part, for the fact that these patients were quite refractory to treatment and that in no case did neurologic medications reduce the hallucinations.

Posttraumatic stress disorder veterans with auditory hallucinations had significantly higher combat exposure scores than other veterans, suggesting that severe or prolonged trauma contributes to the development of hallucinations in some persons. We have seen patients with extreme degrees of combat exposure who did not report hallucinations. Perhaps the combination of prolonged, intense combat stimuli, coupled with a physiologically based heightened arousability, would account for this phenomenon. Research conducted by Kolb (11, 12) has suggested the existence of a subtype of posttraumatic stress disorder that is characterized by increased physiological responding and heightened startle responses. This subtype may be similar to that of the veterans with posttraumatic stress disorder and auditory hallucinations, with amount of combat exposure mediating the presence of hallucinatory experiences.

The behavioral treatment of imaginal flooding was partially successful in two of the cases, ineffective in one case, and perhaps iatrogenic in two cases of auditory hallucinations. In contrast, posttraumatic stress disorder veterans with no hallucinations responded more favorably to the flooding treatment but were also more likely to terminate treatment prematurely than were veterans with hallucinations. Since the flooding treatment requires patients to conjure up and concentrate on covert imaginal stimuli, the increased cognitive dysfunction of posttraumatic stress disorder veterans with auditory hallucinations may have limited their ability to attend to images long enough to extinguish the anxiety.

These observations are preliminary but suggest that the presence of auditory hallucinations in posttraumatic stress disorder may indicate relatively specific etiological and treatment factors. Continued research in this area is needed to answer these questions.

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Discontinuation of Alprazolam Treatment in Panic Patients

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Alprazolam treatment was tapered in 17 panic patients at a rate of 10% of the starting dose every 3 days. Only four subjects completed withdrawal on schedule (4–5 weeks); four additional subjects discontinued treatment in 7–13 weeks. During withdrawal 15 patients had recurrent or increased panic attacks and nine had significant new withdrawal symptoms. Most common among the latter were malaise, weakness, insomnia, tachycardia, lightheadedness, and dizziness. None had seizures, psychosis, or significant neurological or EEG abnormalities. Results indicate that relapse and withdrawal are important considerations in the choice of alprazolam treatment for panic attacks.
(Am J Psychiatry (1987; 144:303–308)

The triazolobenzodiazepine alprazolam is a new, effective antipanic agent (1–3). Alprazolam's rapid action and low side effect profile make it an important therapeutic addition. However, what happens when alprazolam is discontinued is unclear.

When a drug dose is lowered or discontinued, two types of symptoms may appear: those specifically due to drug withdrawal and those which are a recrudescence of the drug-suppressed illness (relapse).

Withdrawal symptoms are highly stereotyped, appear in proportion to daily dose and length of treatment, and disappear with time. In contrast, relapse shows the distinctive illness pattern and does not follow a course of temporary exacerbation followed by normalization. However, distinguishing between withdrawal and relapse in anxiety patients may be difficult, since some anxiety symptoms are often part of the withdrawal pattern.

Benzodiazepine withdrawal studies in anxious patients without panic disorder indicate that many have symptom recurrence or a withdrawal syndrome. Over 50% of patients whose drugs are discontinued experience symptoms such as insomnia, agitation, anxiety, tremor, irritability, headache, nausea, and dizziness (4–10). Recurrence of symptoms of illness at greater than pretreatment levels (rebound) has also been described (4, 8).

Abrupt benzodiazepine discontinuation can cause seizures (11, 12). Three cases of grand mal seizures on abrupt cessation of alprazolam have been reported (13, 14).

Here we will describe tapered alprazolam discontinuation in panic disorder patients. Specific questions we addressed were as follows: 1) Does tapered discontinuation of alprazolam induce a withdrawal syndrome? If so, what are its characteristics? 2) Does alprazolam discontinuation affect frequency and severity of panic attacks? 3) Does the illness become reestablished? 4) Can withdrawal be successfully completed without adjunctive treatment?

METHOD

The 18 withdrawal study subjects were drawn from 30 treatment study patients (3). Twelve patients did not enter; six had terminated treatment before the withdrawal study, three developed major depressive disorder, and three refused to participate.

All 18 subjects had *DSM-III* panic disorder or agoraphobia with panic attacks. Subjects were between 18 and 60 years old and without serious medical illnesses, current *DSM-III* major depression, or alcohol or drug abuse in the past 6 months. Subjects were largely self-referred outpatients. Results of physical examination, CBC, blood chemistries, thyroid profile, EKG, EEG, and urinalysis were normal at baseline. Written informed consent was obtained from all subjects.

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Supported in part by NIMH grants MH-33422 and MH-30906 and Research Scientist Development Award MH-00416 (Dr. Gorman) and by the Upjohn Company.

The authors thank Dr. Timothy Pedley for assistance in the neurological evaluation of patients and Mr. Tom Cooper for assay of alprazolam plasma levels.

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All 18 subjects participated in a 13-week treatment study (3). Responders only were scheduled to continue for an additional 12-week maintenance period before withdrawal. Therefore responders underwent withdrawal after a minimum of 24 weeks and nonresponders after 12–16 weeks of drug treatment.

Alprazolam was decreased every 3 days at as close to a rate of 10% of the original dose as was permitted by 0.5 mg tablets. The goal was to discontinue medication in 30 days.

Each week patients received separate packets for each dose of the upcoming week. As the dose decreased, active medication was replaced by indistinguishable placebo. Therefore, the number of daily tablets remained constant. Patients were told about the taper, but the rate was kept from them.

Patients also received an emergency bottle containing fifteen 0.5 mg alprazolam tablets. If a patient called between visits in significant distress, the treating psychiatrist could give an additional emergency dose of active alprazolam. If more than one extra dose was needed during a week, the patient was removed from the protocol at the next visit and a slower open withdrawal schedule was begun. Patients were also removed from the protocol at scheduled visits if they were so symptomatic that fixed tapering was hazardous. If even slow tapering led to a relapse, an alternative antipanic drug (e.g., imipramine) was started or alprazolam was increased to an effective level.

Research psychiatrist clinical assessment, neurological examination, and EEG were done before treatment, one day before withdrawal, and weekly during withdrawal.

Patients kept a record of anxiety symptoms. The number of panic attacks was recorded at weekly visits; in this report, spontaneous and situational panic attacks were combined. Clinical condition was rated on two panic and phobic scales that measured severity and change. The five factors measured were panic attacks, anticipatory anxiety, phobic avoidance, functional impairment, and overall clinical condition. These factors were rated on a 7-point scale (1=normal or markedly improved, 4=moderate or no change, 7=among the most seriously ill or markedly worse). Ratings for panic attacks combined frequency and intensity.

Withdrawal symptoms and side effects were rated on a scale containing 32 items that frequently accompany benzodiazepine withdrawal. Items were rated on a 4-point scale (0=none, 3=severe). For each subject the average number of *new* withdrawal symptoms was determined as follows: all scores for symptoms on the symptom and side effect scale that the subject had not had at more than a mild level (score=0 or 1) before withdrawal but had at least moderately (score=2 or 3) during withdrawal were added together, and this sum was then divided by the number of withdrawal protocol weeks. Two subjects (patients 7 and 10) had incomplete scale ratings. Symptoms described in their charts as new during alprazolam discontinuation were considered withdrawal symptoms; however, withdrawal scores were not calculated.

Neurological examinations were done by a Board-certified neurologist or a senior neurology fellow working under the latter's supervision. Blood samples for determination of alprazolam plasma levels were drawn weekly during withdrawal in a subgroup of patients. Levels were assayed by gas liquid chromatography according to the method of Greenblatt et al. (15).

RESULTS

Sixteen of the 18 subjects responded to alprazolam: 14 in the acute treatment study and two (subjects 3 and 16) during maintenance (see table 1). Mean length of drug treatment before withdrawal was 29.4 weeks (range, 23–42 weeks) for patients who entered the maintenance phase (acute treatment responders) and 14.75 weeks (range, 12–20 weeks) for those who did not (acute treatment nonresponders). Mean drug dose at the start of withdrawal was 5.25 mg/day (range, 2.5–8.0 mg/day) for acute responders and 6.0 mg/day (range, 3–8.5 mg/day) for acute nonresponders. Sixteen of the 18 subjects were panic free before withdrawal.

Only four of the 18 subjects completed withdrawal from alprazolam by following the fixed protocol (see table 1). Thirteen subjects were unable to complete withdrawal at that rate; seven terminated prematurely because of panic recurrence, five because of a combination of panic recurrence and *new* withdrawal symptoms, and one because of new withdrawal symptoms only. The four successfully tapered patients did not differ on demographic or treatment characteristics from the 13 who failed to follow the protocol.

The 18th subject dropped out in her second tapering week after suicidal ideation following a marital argument. Since panic attacks recurred, her overall discontinuation outcome was unsuccessful; however, she was excluded from other analyses. (Her exclusion left 15 subjects who were panic free before withdrawal.)

Fifteen of the 17 patients had a recurrence or increase in panic attacks during discontinuation compared to their prediscontinuation status. One (subject 4) had a similar frequency of panic attacks before and during tapering. Only one patient (subject 11) had no panic attacks.

Eight of these 15 patients who relapsed (subjects 1, 2, 3, 6, 8, 12, 14, and 16) had mild to moderate panic symptoms. In this group, the average weekly number of panic attacks during tapering was 1.5 or less (see table 1). Typically these patients had one or two panic attacks a week for 1 or 2 weeks. Three subjects (1, 2, and 3) of the four patients who completed the protocol were in this group; the fourth (subject 4) had no change in panic attacks during tapering.

In contrast, the other seven patients (subjects 5, 7, 9, 10, 13, 15, and 17) constituted a "severe panic relapse" group. All but one (subject 5) averaged more

TABLE 1. Characteristics of Panic Patients Who Did and Did Not Successfully Discontinue Alprazolam Treatment

Group and Subject	Age (years)	Sex	Response to Acute Alprazolam Treatment	Alprazolam Dose (mg/day)		Weeks		Number of Panic Attacks: Week Before Continuation	Discontinuation		New Withdrawal Symptoms[c]	
				Start[a]	End	Alprazolam[a]	Discontinuation		Total	Weekly Average[b]	Weekly Average	Specific Symptoms
Successful												
1	38	M	Yes	6.0	0	36	4	0	1	0.25	0	None
2	37	M	Yes	6.5	0	30	5	0	4	0.80	4.0	Insomnia, lightheadedness, confusion, dizziness, faintness, decreased appetite
3	26	F	Yes	7.0	0	20	5	0	1	0.20	10.4	Dizziness, lightheadedness, fatigue, ataxia, irritability, depression, tremor, weakness, sweating, diarrhea, headaches, constipation, nasal congestion, blurred vision
4	23	F	No	5.5	0	14	5	2	4	0.80	3.2	Nausea, malaise, rigidity, constipation, difficulty urinating
Unsuccessful												
5	53	F	Yes	2.5	1.0	32	4	0	4	1.00	3.7	Malaise, increased appetite
6	35	F	Yes	3.0	2.0	23	2	0	3	1.50	6.0	Insomnia, lightheadedness, tachycardia, fatigue, confusion, dizziness, impaired mentation
7	43	M	Yes	3.5	3.0	27	1	0	4	4.00	—	Jitteriness, restlessness, sweating, difficulty concentrating[d]
8	32	M	Yes	4.0	0.5	29	4	0	1	0.25	2.0	Nausea, malaise, excitement/nervousness
9	42	M	Yes	4.0	0.5	35	4	0	23	5.80	2.0	Diarrhea, tachycardia, insomnia, loss of appetite
10	31	M	Yes	4.5	3.5	40	1	0	3	3.00	—	Malaise[d]
11	32	F	Yes	8.0	5.0	24	2	0	0	0	3.0	Blurred vision, tachycardia, weight loss
12	32	M	Yes	5.0	0.5	26	4	0	1	0.25	3.0	Insomnia, malaise, ataxia, impaired mentation
13	33	F	Yes	5.0	2.0	36	3	0	7	2.30	4.3	Faintness, tachycardia, irritability, depression, weakness
14	22	M	Yes	7.0	5.0	33	2	0	2	1.00	3.0	Depression, faintness, weakness
15	39	M	Yes	8.0	5.0	47	2	4	6	3.00	0	None
16	42	F	No	3.0	1.5	13	2	0	1	0.50	4.0	Headaches, sedation, confusion, weakness, sweating
17	30	M	No	8.5	2.5	12	4	0[e]	3	7.80	2.2	Rash, dry mouth, sweating

[a]Before start of discontinuation.
[b]Total spontaneous and situational panic attacks reported during discontinuation divided by number of weeks in discontinuation.
[c]See Method section for definition.
[d]No rating; data from clinical chart.
[e]Subject 17 had five partial but no full panic attacks during prewithdrawal week.

than two panic attacks a week (range, 2.3–7.8) during withdrawal (see table 1). Subject 5 had a lower score (1.0) because her first 3 panic-free withdrawal weeks reduced the impact of her fourth week, in which four severe attacks led to alteration of her withdrawal schedule. Subject 15 had a dramatic increase in the intensity (but not the frequency) of panic attacks. In this group, calls to request a medication increase between visits were frequent. All subjects had several weeks when they experienced several panic attacks each week. Four (subjects 7, 9, and 17 during the protocol and subject 15 after the protocol) had a frequency and severity of panic attacks during withdrawal that exceeded pretreatment levels. The possible persistence of this "rebound" effect could not be evaluated, since treatment was reinstituted soon afterward in view of the patient's disturbance.

Before the tapering of alprazolam, 10 of 17 patients were rated well or only minimally ill on the "overall" item of the Panic and Phobia Severity Scale; however, at termination from the protocol none of the patients was rated completely recovered, and only two were well enough to be rated minimally ill.

Table 2 lists newly emergent withdrawal symptoms reported by at least three patients. The most commonly reported symptoms were quite similar to those

TABLE 2. Commonly Reported Alprazolam Withdrawal Symptoms in 15 Panic Patients[a]

Symptom	Patients Reporting Symptom: During Discontinuation Only N	%	During Pretreatment and Discontinuation N	%
Malaise	4	27	1	7
Weakness	4	27	1	7
Insomnia	4	27	3	20
Tachycardia	4	27	2	13
Dizziness	3	20	3	20
Lightheadedness	3	20	2	13
Faintness	3	20	1	7
Confusion	3	20	0	0
Excessive sweating	3	20	1	7
Depression	3	20	0	0
Irritability	2	13	1	7

[a]Two of the 17 subjects were not included because of incomplete ratings; patient 7 had no pretreatment ratings, and patient 10 no termination ratings.

typically reported during benzodiazepine withdrawal. However, seizures, psychotic symptoms, organicity, delirium, and syncope did not occur.

Fourteen of the 17 subjects reported at least two newly emergent withdrawal symptoms. One (subject 10) reported only one such symptom, and two (subjects 1 and 15) reported none. Table 1 lists the specific symptoms reported.

Six of the 15 symptomatic patients (subjects 8–11, 14, and 17) had mild to moderate withdrawal symptoms: either 1–2 weeks of moderate discomfort with several symptoms or 3–4 weeks with one symptom. The remaining nine patients (subjects 2–7, 12, 13, and 16) had more severe symptoms: either 1–2 weeks of considerable discomfort and numerous symptoms or persistent moderate difficulty with several symptoms over 3–4 weeks. Most patients had considerably more complaints than is reflected by the first column of table 2, since any symptom that also occurred during treatment was excluded from this list. The second column of table 2 lists the frequency with which these latter symptoms occurred.

Weekly neurological examinations were completed on 10 subjects, including six of the nine with severe withdrawal symptoms. Two subjects had mild hand tremors at one examination—one had hyperflexia and one mild ataxia. There were no other neurological abnormalities.

Weekly EEG recordings were completed on 10 subjects, including five of the nine with severe withdrawal. Two had excessive slowing on one EEG examination. Both abnormalities occurred in the postprotocol phase. All other EEGs were normal. None had spikes, sharp waves, or any signs suggestive of seizure activation.

Weekly alprazolam plasma levels of eight subjects during withdrawal showed sequential decreases paralleling dosage. Two subjects refused to participate in this aspect of the study because of needle phobia. Levels of the remaining eight patients were not measured regularly because of scheduling difficulties.

Ten of the 13 patients who did not complete alprazolam withdrawal during the protocol continued withdrawal at slower rates. Formal clinical ratings continued during this phase. Four of these patients (subjects 7, 9, 10, and 16) discontinued alprazolam. Their total tapering times were 7, 12, 13, and 6 weeks, respectively. Therefore, a total of eight of 17 patients completed alprazolam withdrawal by simple tapering of dose and support. Six additional patients attempted to taper alprazolam at rates of 0.5 mg–0.25 mg/week. All stopped because they were unwilling to tolerate persistent panic symptoms. All six started tricyclic antidepressants while taking 0.5–2.0 mg/day of alprazolam.

Of the eight patients who discontinued alprazolam treatment and did not take other antipanic medication (four during and four after the protocol), six were followed for 3–5 months after medication was discontinued. Three subjects (2, 9, and 16) remained well (no or very occasional panic attacks). One (subject 7) relapsed immediately, one (subject 1) at 4 months, and one (subject 4) at 5 months.

DISCUSSION

Does Alprazolam Induce Withdrawal, and If So, What Are Its Characteristics?

Fourteen of our 17 subjects experienced at least two new withdrawal symptoms during alprazolam discontinuation. In half (nine of 17), symptoms were considered severe. However, there were no medically dangerous effects, and only one subject left the protocol because of withdrawal symptoms alone.

The new withdrawal symptoms observed were similar in type to those described in previous studies of withdrawal from therapeutic doses of benzodiazepines (4–10).

The rate of new withdrawal symptoms in our patients appears higher than rates reported in previous studies of benzodiazepine discontinuation. However, accurate comparisons are difficult. Earlier studies differed from ours with respect to subject diagnosis, length of drug treatment, history of previous benzodiazepine use, rate of drug decrease, and drug half-life. Since all of these factors affect severity of withdrawal symptoms, study variation may explain the observed differences.

What Effect Does Alprazolam Discontinuation Have on Frequency and Severity of Panic Attacks?

Our most striking finding was the rapid recurrence or increase of panic attacks in most of our patients (15 of 17 subjects, 14 of 15 subjects who were panic free). DuPont and Pecknold (16) have presented similar results from a withdrawal study of 60 panic patients

treated with alprazolam for 8 weeks. In that study 89% (32 of 36) of panic-free patients had panic recurrence during withdrawal.

The rates of panic recurrence during alprazolam discontinuation observed by ourselves and DuPont and Pecknold appear considerably higher and more rapid in onset than those seen in panic patients tapered from tricyclic antidepressants (17) or monoamine oxidase (MAO) inhibitors (18). If confirmed, this finding may indicate that alprazolam discontinuation can precipitate panic attacks in panic patients. Another possibility is that this finding reflects the difference between the rapid elimination of alprazolam compared to the longer-lived effects of MAO inhibitors and tricyclic antidepressants, although the latter are not well documented. Additional alternative explanations might be differences between drug antipanic mechanisms or an as yet undetected distinction between high- and low-potency benzodiazepines.

Further studies including comparison of panic and nonpanic patients during withdrawal of alprazolam and other benzodiazepine as well as nonbenzodiazepine compounds are necessary to address this question.

Transient Flare-Up Versus Relapse: Does the Illness Become Reestablished?

We are not able to determine whether the panic relapse during alprazolam discontinuation reflected a transient flare-up or a persistent relapse. For ethical reasons, 10 of our subjects either did not discontinue alprazolam or started treatment with another antipanic medication within a few weeks of or before discontinuing alprazolam. However, of the six subjects who were medication free after the protocol, three remained panic free for 1–5 months and two had only infrequent panic attacks that did not require treatment.

DuPont and Pecknold (16) stated that while 73% of their patients had panic attacks during medication tapering, only 54% still had panic attacks 2 weeks after medication discontinuation. This, together with our findings, suggests that in some patients, recurrence of panic attacks may be temporary. However, the numbers are too small and follow-up too inconsistent for firm conclusions.

Can Discontinuation Be Successfully Completed Without the Use of Adjunctive Medication?

Our data suggest that with a 10% decrease rate, adjunctive medication may be required to successfully complete alprazolam discontinuation in at least one-third of panic patients. Six of our 17 patients required adjunctive use of tricyclic antidepressants in order to complete tapering of alprazolam. DuPont and Pecknold indicated that a firm attitude on the part of the investigator generally increased the number of patients who successfully discontinued medication. Our goal was to take patients off the medication. However, since the possible consequences of alprazolam discontinuation are relatively unknown, we did tend to be cautious when confronted with a patient in significant distress.

One approach is to slow the tapering rate as discussed earlier. An alternative strategy is to discover a rapidly acting drug that blocks relapse if taken during drug discontinuation.

Klein has proposed a possible explanation of the rapid panic recurrence and withdrawal symptoms observed during alprazolam discontinuation (personal communication). He speculated that alprazolam exerts its antipanic effect by blocking afferent pathways to the locus ceruleus or other noradrenergic centers. Massive deafferentiation usually produces receptor hypersensitivity distal to the point of blockade (19). In this case, discontinuing alprazolam treatment would be expected to leave these hypothetical noradrenergic center receptors hypersensitive and prone to overresponse.

If this model is accurate, giving patients whose alprazolam treatment is being tapered off a quick-acting α_2 agonist such as clonidine might prevent symptomatic exacerbation during withdrawal. Clonidine decreases locus ceruleus firing by stimulating presynaptic inhibitory receptors (20, 21).

Limitations and Conclusions

This study has several major limitations. Most significant is the lack of a double-blind placebo control design. It is impossible to assess the degree to which a patient's anxiety about alprazolam discontinuation contributed to withdrawal symptoms or requests to stop discontinuation. Less severe benzodiazepine withdrawal symptoms have been reported in placebo-treated patients withdrawn in a double-blind manner compared to those openly withdrawn (22).

Incomplete compliance data are a second problem. For 10 subjects there were no compliance data. We cannot rule out the possibility that the mildness of their withdrawal symptoms was due to augmentation of the protocol regimen by nonprotocol drugs. Future studies should include systematic urine toxicology data to rule out this possibility.

Ratings were done at the patients' scheduled weekly visits. If a patient became symptomatic and requested a dose increase between visits, by the time the formal rating occurred the most severe withdrawal effects had been blunted. The week's rating was an average of these events. The ratings may therefore have underestimated the severity of symptoms.

Our findings indicate that relapse, withdrawal symptoms, symptomatic exacerbation, and possible adjunctive medication during tapering must be major considerations in deciding whether to use alprazolam for the treatment of panic attacks. Further studies, including direct comparisons to tapering with other antipanic agents, variations in rate of alprazolam decrease, and

the use of adjunctive medications, are necessary before alprazolam's therapeutic role can be fully assessed.

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The Significance of Past Mania or Hypomania in the Course and Outcome of Major Depression

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Patients with primary major depression (N=372) were followed for 2 years to determine the prognostic importance of past manic or hypomanic episodes. While bipolar I and bipolar II patients were more likely to relapse and bipolar I patients were more likely to attempt suicide, these patients resembled nonbipolar depressed patients in likelihood of recovery and psychosocial impairment in various areas. Compared to nonbipolar patients, those with bipolar I depression were much more likely to develop mania, while bipolar II patients were more likely to develop hypomania. Cycling during the index episode predicted a relatively low likelihood of recovery for bipolar I patients but had no apparent prognostic significance for patients with bipolar II illness.

(Am J Psychiatry 1987; 144:309–315)

The distinction between bipolar and unipolar depression has widely acknowledged practical significance, since patients with bipolar depression are much more likely to suffer recurrences (1) and to benefit from lithium in both acute (2, 3) and prophylactic (4) phases of their treatment. Beyond this, however, little is known of what a history of mania means for a depressed patient. Specifically, do the symptomatic and psychosocial outcomes of bipolar depression differ from those of unipolar depression, given the availability of contemporary therapies?

A similar question applies to those patients who fall clearly in neither the bipolar nor the unipolar group. Such patients report past syndromes with some of the features typical of mania but which lack the number or duration of symptoms or the severe impairment associated with a manic syndrome. Researchers have not reached consensus on the nosologic status of such patients and have generally separated them from bipolar and unipolar patients to preserve diagnostic homogeneity. However, recent data suggest that this indeterminant, or bipolar II, group may be other than simply a mixture of bipolar I and nonbipolar patients. When compared to relatives with bipolar I or nonbipolar major depression, relatives with bipolar II major depression had the earliest age at onset and the highest rate of nonserious suicide attempts, marital disruption, and psychopathology in the month preceding assessment (5). Thus, we predicted bipolar II probands would have a relatively low likelihood of recovery and a greater likelihood of psychosocial morbidity during follow-up. Moreover, family study data (6) showed that bipolar II illness loaded heavily in the families of bipolar II probands, suggesting that the diagnosis would be stable over time and that hypomania would not prove to be simply an early stage of bipolar I illness. Finally, recent findings (7) indicate that cycling within the index episode is a powerful predictor of time to recovery in bipolar I illness. While this does not lead to a specific prediction for bipolar II depression, the effects of cycling on outcome should be considered in that condition as well.

With the above questions and predictions in mind, we undertook 2-year follow-up comparisons between depressed patients with a history of mania, depressed patients with a history of hypomania, and depressed patients with no history of either mania or hypomania.

METHOD

Raters at each of five university centers recruited both inpatients and outpatients as part of the National Institute of Mental Health Clinical Research Branch Collaborative Program on the Psychobiology of Depression: Clinical Studies Project (8). Of the 339 nonbipolar, 44 bipolar II, and 30 bipolar I patients who entered the study, 89.4% (N=303), 90.9% (N=40), and 96.7% (N=29), respectively, completed a 2-year follow-up. The nonbipolar patients described here had had no prior episodes of mania or hypomania as defined by the Research Diagnostic Criteria (RDC) (9). The 40 bipolar II patients had had hypomania, either during the index episode or before, but had

Received Feb. 10, 1986; revised July 7, 1986; accepted Aug. 18, 1986. From the NIMH Clinical Research Branch Collaborative Program on the Psychobiology of Depression: Clinical Studies. Address reprint requests to Dr. Coryell, Department of Psychiatry, University of Iowa College of Medicine, 500 Newton Rd., Iowa City, IA 52242.

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never had mania; the 29 bipolar I patients had had mania at some time before intake and may or may not have had separate episodes of hypomania. All 372 patients met the RDC for major depression at intake; this was assured by the exclusion of those with mixed episodes. Also excluded were patients with secondary depression. Some patients had had a prior episode of schizoaffective disorder, but none had this diagnosis during the index episode.

Patients were further divided as to whether or not they had cycled before intake. Bipolar I patients were judged to have cycled if the index episode included mania and bipolar II patients if the index episode included hypomania. Thus 16 bipolar I and 17 bipolar II patients had cycled at intake, whereas 13 bipolar I and 23 bipolar II patients had not.

Baseline assessment incorporated information from direct patient interview, informants, and medical records and was codified in a battery of instruments that included the Schedule for Affective Disorders and Schizophrenia (SADS) (10). All raters underwent systematic training in the use of these instruments through the use of videotapes, case vignettes, and cross-center training sessions. The raters did not systematically share their diagnostic conclusions with the treating physicians, nor were they prohibited from doing so.

Following discharge, raters recontacted probands at four subsequent 6-month intervals and administered the Longitudinal Interval Follow-Up Evaluation (LIFE) (7, 11), either by telephone or in person. This interview provided ratings for both nonaffective and affective psychopathology and for resulting psychosocial impairment in a variety of areas. Both inpatient and outpatient records were sought, and the resulting information was incorporated into these ratings. The present analyses include only those patients who completed 2 years of follow-up, with the exception of the life-table analyses; this included all patients with at least a 6-month follow-up. Thus, the numbers listed in figures 1 and 2 are larger than those in tables 1 and 2.

In the present report recovery from the index episode required that criteria symptoms for major depression had been absent (or present to no more than a slight degree) for at least 8 consecutive weeks during the follow-up period. Recovered patients had to have been similarly free of manic and hypomanic symptoms during that minimum 8-week period. Many of those who did not recover from the index episode experienced a sustained partial remission; that is, symptom number and intensity during the best 8-week period fell far short of satisfying the criteria for major depression, although symptom resolution was insufficient for a rating of "recovered" as defined earlier. Recovered patients were divided into those who recovered completely (had no symptoms whatsoever for at least 8 weeks) and those who had one or two mild symptoms during their best 8-week period. A new episode required, first, that the subject had recovered from the index episode and then met the full criteria for major depression, mania, schizoaffective disorder, hypomania, or minor depression.

Shifts in polarity to hypomania or mania indicated that the subject met the respective RDC for these disorders after intake. An episode of hypomania was identified in the following analysis only if it was not contiguous with an episode of mania.

The Global Assessment Scale (GAS) score represented a composite rating of psychopathology and resulting psychosocial impairment. Specific areas of psychosocial impairment during follow-up were quantified as the proportion of subjects manifesting mild to severe impairment at work, in relationships with friends, in their general level of satisfaction or contentment, and in overall adjustment as judged by the rater and recorded in the LIFE (11). To aid comparisons with earlier reports (12), we have focused on impairment at two points during follow-up—at 6 months and 2 years.

Treatment was also monitored at each follow-up interval and qualified in the LIFE, with the dose of each drug recorded in longitudinal fashion. To condense the resulting data to a usable form, drug equivalencies were subsequently determined by reference to the relevant literature. (These data are available from the authors on request.) Thus, 150 mg of imipramine were considered the equivalent of 75 mg of nortriptyline and 300 mg of chlorpromazine the equivalent of 6 mg of haloperidol.

We undertook group comparisons in several steps. In the first, we compared all three groups for each variable of interest. Statistically significant results were further explored with pairwise comparisons, first between bipolar I and nonbipolar groups, then between bipolar II and each of the other two groups. Thus, results will be presented in this order.

For most categorical comparisons we used the chi-square statistic, but for 2×2 comparisons with any expected value less than 5, we used Fisher's exact test. Analysis of variance was used to compare continuous variables. The number of comparisons made here raised the likelihood that some statistically significant differences occurred by chance. Our interpretation of a given statistically significant comparison therefore depended on the level of significance and whether such a finding was predicted by earlier work.

RESULTS

Bipolar I Versus Nonbipolar Patients

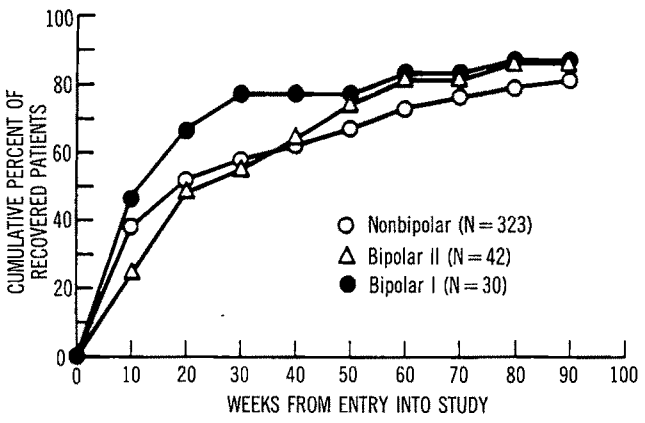
Bipolar I patients did not differ significantly from nonbipolar patients on any of the baseline measures considered; 58.6% (N=17) of the 29 bipolar I patients and 66.3% (N=201) of the 303 nonbipolar patients were women, and the mean±SD ages were 37.0±13.9 and 40.4±15.6 years, respectively. These two groups had similar distributions of marital status and social class. Moreover, 79.3% of the bipolar I and 71.9% of

TABLE 1. Clinical Outcome of Nonbipolar, Bipolar II, and Bipolar I Patients During a 2-Year Follow-Up

Outcome	Nonbipolar			Bipolar II			Bipolar I		
	Available N	With Outcome		Available N	With Outcome		Available N	With Outcome	
		N	%		N	%		N	%
Recovered from index episode	303			40			29		
By 6 months		173	57.1		21	52.5		22	75.9
By 24 months		249	82.2		35	87.5		25	86.2
Not recovered by 2 years	54			5			4		
No sustained partial remission		17	31.5		1	20.0		1	25.0
Recovered by 2 years	249			35			25		
Incomplete recovery		65	26.1		7	20.0		4	16.0
Relapsed[a]		107	43.0		27	77.1		16	64.0
More than one subsequent episode[b]		21	8.5		10	28.5		5	20.0
Hospitalized at intake	218			26			23		
Rehospitalized		86	39.4		15	57.7		13	56.5
Rehospitalized more than twice		19	8.7		5	19.2		3	13.0
"Significant" nonaffective psychopathology	303	114	37.6	40	14	35.0	29	9	31.0
Suicide attempt[c]	303	31	10.2	40	7	17.5	29	7	24.1
Shifts in polarity	339			44			30		
At least one manic episode[d]		7	2.1		2	4.5		13	43.3
At least one hypomanic episode not contiguous with a manic episode[e]		16	4.7		9	20.5		13	43.3

[a]Significant difference among groups (χ^2=17.0, df=2, p<.001), between bipolar I and nonbipolar patients (χ^2=4.1, df=1, p<.05), and between bipolar II and nonbipolar patients (χ^2=8.5, df=1, p<.005).
[b]Significant difference among groups (χ^2=13.8, df=2, p<.005) and between bipolar II and nonbipolar patients (p=.002, Fisher's exact test).
[c]The mean±SD level of psychological seriousness of the most serious attempt was 2.80±1.21 for the nonbipolar group, 3.14±1.21 for the bipolar II group, and 4.00±1.73 for the bipolar I group; there was a significant difference among the groups (F=3.69, df=2, 369, p<.03, three-way analysis of variance) and between the bipolar I and nonbipolar patients (p<.05, Tukey follow-up tests). The mean number of suicide attempts was 0.19±0.77 for the nonbipolar group, 0.40±1.06 for the bipolar II group, and 0.93±2.58 for the bipolar I group; there was a significant difference among the groups (F=6.33, df=2, 369, p<.002, three-way analysis of variance) and between the bipolar I and nonbipolar patients (p<.05, Tukey follow-up tests).
[d]Significant difference among groups (χ^2=93.1, df=2, p<.0001), between bipolar I and bipolar II patients (χ^2=16.6, df=1, p<.0001), and between bipolar I and nonbipolar patients (χ^2=91.6, df=1, p<.0001).
[e]Significant difference among groups (χ^2=56.6, df=2, p<.0001), between bipolar I and nonbipolar patients (χ^2=56.7, df=1, p<.0001), between bipolar II and nonbipolar patients (χ^2=15.8, df=1, p<.0001), and between bipolar II and bipolar I patients (χ^2=4.5, df=1, p<.05).

FIGURE 1. Recovery of Nonbipolar, Bipolar II, and Bipolar I Patients From Index Episode



the nonbipolar patients were inpatients, and they had similar baseline GAS scores (38.8±13.0 and 43.0±12.2, respectively).

The bipolar I and nonbipolar groups also resembled each other in the likelihood of recovery by 6 months and 2 years (table 1) and by the time elapsing before that recovery (figure 1). Other events did distinguish these groups, however; bipolar I patients were more likely to relapse and to have multiple subsequent episodes. Moreover, bipolar I patients made more suicide attempts, and these attempts were, on the average, more psychologically serious (the intent to die was judged to have been greater).

At 6 months bipolar I patients were significantly more likely than nonbipolar patients to report work impairment (71.4% [N=10] of 14 rated versus 30.6% [N=19] of 62; χ^2=9.2, df=1, p<.005). None of the other psychosocial measures distinguished these groups at 6 months, nor were there consistent trends favoring either group. Group differences in the proportion with work impairment narrowed considerably by 2 years; six of 18 (33.3%) of the bipolar I and 55 of 206 (26.7%) of the nonbipolar patients reported impairment at this time. Again, none of the other psychosocial outcome measures distinguished these groups. On almost all measures, both groups showed substantial improvement between the 6- and 24-month follow-up.

The most striking group difference was in the nature of new episodes (table 1); bipolar patients were more than 20 times more likely to develop mania during the 2 years of follow-up than were nonbipolar patients. Noncontiguous hypomanic episodes were roughly 10 times more likely to occur among bipolar I patients.

Patients in these two groups were equally likely to

receive a course of ECT or a trial of tricyclic antidepressants during the 2 months after intake. Approximately 25% of the patients in each group received aggressive tricyclic antidepressant therapy—the equivalent of 200 mg/day or more of imipramine for at least 4 weeks—and less than 20% in each group received a total of five or more ECTs. Nonbipolar patients were significantly less likely to receive lithium than were bipolar I patients; 7.3% (N=20) and 77.8 (N=21), respectively, received lithium for at least 2 of the first 8 weeks of follow-up (χ^2=103.4, df=1, p<.0001). Similar patterns emerged at weeks 25 and 50. The proportions of each group receiving aggressive tricyclic antidepressant therapy, as defined earlier, were not significantly different at either time, while at both times approximately 8% of nonbipolar patients and 60% of bipolar I patients were taking lithium.

Bipolar II Versus Bipolar I and Nonbipolar Patients

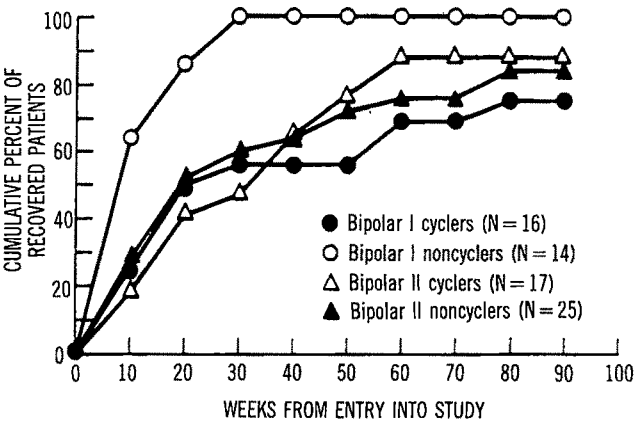
The mean±SD age of the bipolar II patients at intake was 39.2±15.6 years, and 62.5% (N=25) were women. The bipolar II patients further resembled patients in the other two groups by marital status, social class, the proportion who were inpatients, and mean baseline GAS score (41.1±11.7).

While the subsequent time to recovery did not distinguish bipolar II patients (figure 1), they were most likely to have multiple subsequent episodes and rehospitalizations (table 1). By various measures of suicidal behavior, bipolar II patients took an intermediate position between the other two groups; the measures of psychosocial outcome failed to significantly distinguish bipolar II patients, just as they failed to distinguish bipolar I from nonbipolar patients.

In contrast, the phenomenology of subsequent episodes showed sharp group differences (table 1). While bipolar II patients were twice as likely as nonbipolar patients to meet the criteria for mania during follow-up, this was still uncommon and occurred in less than 5% of cases. However, bipolar II patients were four times as likely to develop a subsequent episode of hypomania as were nonbipolar patients, although this outcome was not nearly as likely as the development of mania among bipolar I patients.

During the first 2 months of follow-up, 33.3% (N=13) of the bipolar II patients received the equivalent of 200 mg/day or more of imipramine for at least 4 weeks, while 18% (N=7) received a course of five or more ECTs. These figures were quite similar to those for bipolar I and nonbipolar patients. During this same period, 26% (N=10) received lithium for 2 or more weeks; this figure was significantly greater than that for nonbipolar patients (χ^2=14.8, df=1, p<.001) and significantly less than that for bipolar I patients (χ^2=132.2, df=1, p<.0001). The proportions of bipolar II patients receiving the equivalent of 200 mg/day or more of imipramine at weeks 25 and 50 were also nonsignificantly different from the corresponding proportions among bipolar I and nonbipolar patients. The proportions receiving lithium at each of these two times were again intermediate and significantly different from each of the other two groups (week 25: χ^2=53.5, df=2, p=.0001; week 50: χ^2=45.4, df=2, p=.0001).

FIGURE 2. Recovery of Bipolar I and Bipolar II Cyclers and Noncyclers From Index Episode



Effects of Cycling

Cycling before intake strongly influenced the likelihood of recovery during follow-up for bipolar I but not for bipolar II patients (figure 2). Time to recovery varied significantly by group (χ^2=9.71, df=1, p=.0018, Gehan-Wilcoxon rank test), and pairwise follow-up tests yielded significant differences between noncycling bipolar I patients and each of the other three groups (Wilcoxon χ^2=9.7, 11.7, and 10.0 for comparisons between noncycling bipolar I patients and cycling bipolar I, cycling bipolar II, and noncycling bipolar II patients, respectively; df=1, p=.0018, .0006, and .0016, respectively); none of those three groups differed significantly from each other.

These relationships are reflected as well in the psychosocial ratings (table 2). Bipolar I patients who were cycling at intake (had had manic phases within the index episode) were more likely to be impaired in each of the measures at 6 months than were bipolar I patients who had not been cycling, and this difference grew much more striking at 2 years. On the other hand, bipolar II patients who had been cycling (had had hypomanic phases within the index episode) were slightly less likely to be impaired at 6 months on each of the measures than were noncycling bipolar II patients, and there was very little difference between these two groups at 2 years.

None of the treatment measures listed earlier distinguished cycling from noncycling patients either within the bipolar II or the bipolar I group. In the latter group, cycling patients were somewhat less likely to receive a tricyclic antidepressant course than were noncycling patients (20.0% [N=3] versus 46.1% [N=6]), but this trend disappeared at 1 year when 13.3% (N=2) and 7.7% (N=1), respectively, were receiving

TABLE 2. Psychological Outcome at 6 and 24 Months of Bipolar Depressed Patients Who Had or Had Not Cycled at Intake

Outcome	Bipolar II						Bipolar I					
	Cycling			Noncycling			Cycling			Noncycling		
	Available N	With Outcome N	With Outcome %	Available N	With Outcome N	With Outcome %	Available N	With Outcome N	With Outcome %	Available N	With Outcome N	With Outcome %
Work impairment												
At 6 months	8	5	62.5	12	6	50.0	8	7	87.5	6	3	50.0
At 24 months	10	6	60.0	14	4	28.6	10	5	50.0	8	1	12.5
Fair, poor, or very poor relationships with friends												
At 6 months[a]	17	13	76.5	23	15	65.2	16	13	81.3	13	5	38.5
At 24 months[b]	17	11	64.7	23	11	47.8	16	10	62.5	13	2	15.4
Fair, poor, or very poor level of satisfaction or contentment												
At 6 months	17	14	82.4	23	21	91.3	16	14	87.5	13	7	87.5
At 24 months	17	11	64.7	23	13	56.5	16	10	62.5	13	4	30.8
Fair, poor, or very poor overall adjustment												
At 6 months	17	10	58.8	23	17	73.9	16	8	50.0	13	4	30.8
At 24 months[c]	17	7	41.2	23	10	43.5	16	12	75.0	13	3	23.1
Married at intake but separated or divorced at 24 months	10	2	20.0	15	3	20.0	4	1	25.0	7	2	28.6

[a]Significant difference between bipolar I cycling and noncycling patients ($\chi^2=5.6$, df=1, $p<.025$).
[b]Significant difference between bipolar I cycling and noncycling patients ($\chi^2=6.6$, df=1, $p<.025$).
[c]Significant difference between bipolar I cycling and noncycling patients ($\chi^2=6.9$, df=1, $p<.001$).

an equivalent of 200 mg/day or more of imipramine. Cycling bipolar I patients were somewhat more likely than their noncycling counterparts to receive lithium at all three time points; 80.0% (N=12) received a trial during the first 2 months, and 71.4% (N=10) and 60.0% (N=9), respectively, were taking lithium at 25 and 50 weeks. Corresponding figures for the noncycling bipolar I group were 69.2% (N=9), 53.8% (N=7), and 53.8%.

Secondary Depression

Because secondary depression (major depression antedated by one of a discrete list of nonaffective disorders) was somewhat although not significantly more likely among bipolar II subjects, and because nonbipolar patients with secondary depression have lower rates of recovery (13–15) and higher rates of relapse (16), we repeated the earlier analysis without excluding patients with secondary depressions defined by the RDC. Findings were essentially unchanged; bipolar I and bipolar II patients were more likely than nonbipolar patients to relapse and to develop subsequent manic or hypomanic episodes, respectively. Cycling was prognostically important for bipolar I but not for bipolar II patients. No new significant group differences emerged.

DISCUSSION

Previous outcome comparisons between unipolar and bipolar patients have reached inconsistent conclusions (1). Some found that bipolar patients had a worse overall outcome (17–19). Others (20) noted the reverse, while perhaps the majority found no clear or consistent outcome differences (21–24). These earlier studies have been uniform, however, in finding a higher rate of multiple episodes among bipolar patients (1). Most of these studies compared unipolar patients to bipolar patients who, at the beginning of the observation period, had either mania or depression. These studies have generally not subdivided patients by the syndrome in which they began follow-up. We felt it important to do so, since the short-term outcome of mania may differ from that of depression even within individuals who experience both syndromes. Having done this, we found few differences in outcome among patients who were depressed at intake and divided by lifetime polarity. Like most earlier studies, however, we found a significantly higher proportion of multiple episodes among the bipolar I patients.

In another report from the Collaborative Study of Depression, Keller et al. (7) found no difference in time to recovery between patients who entered the study with mania and those who entered with bipolar I depression. In contrast, patients who were cycling at intake were considerably less likely to recover than those who were not. The present report, which narrowed the cycling group to those who were depressed at the beginning of follow-up, reached the same conclusions; patients who had had mania within their index episode were less likely to recover than those whose mania had occurred only in previous episodes. The prognostic importance of cycling during the index episode apparently does not extend to bipolar II depression. The prognostic relationship of the bipolar I

group to either the bipolar II or nonbipolar group thus depends largely on whether patients with bipolar I depression are or are not cycling.

While bipolar II and bipolar I patients remained phenomenologically distinct, they had similar episode frequencies; the bipolar II group was, in fact, the most likely to have multiple episodes and hospitalizations. Thus these data support Dunner (25), who found the highest rate of rapid cycling (four or more episodes in a 2-year period) among bipolar II patients.

In other respects, outcome for bipolar II patients was not substantially different than that for either bipolar I or nonbipolar patients. The follow-up of probands who were depressed at intake therefore did not support the predictions generated from a study of ill relatives. In particular, bipolar II patients were no less likely to recover and no more likely to make suicide attempts, develop nonaffective morbidity, separate or divorce, or manifest psychosocial impairment in general. Psychopathology in ill relatives, however, was viewed retrospectively over a lifetime and cross-sectionally at a random point in the subject's life. In contrast, the proband follow-up considered developments only during the 2 years after treatment for a primary major depressive episode. The immediate effects of a depression requiring hospitalization or outpatient treatment may extend for some time and obscure group differences that might otherwise be apparent and that might, after all, take a much longer period to manifest. Thus these findings are not necessarily inconsistent with those arising from the study of ill relatives; they do, however, suggest that distinctions based on lifetime polarity will not be helpful in predicting recovery or psychosocial outcome over the short run after treatment for major depression.

These distinctions do predict phenomenological outcome, however. Depressed patients entering treatment with no history of mania appear unlikely to develop mania during the subsequent 2 years whether or not they have experienced hypomania in the past. Bipolar II patients are clearly more likely to develop hypomania, on the other hand, and a bipolar I depressed patient is substantially more likely to develop mania. In fact, over half of these patients developed a manic episode during the 2 years after treatment for major depression.

The history of mania and hypomania used to classify these patients at intake also apparently influenced treatment, since bipolar II patients wee significantly more likely than were nonbipolar patients to be taking lithium at various points during the follow-up period. The diagnostic uncertainty associated with bipolar II disorder probably accounts for the fact that these patients were, in turn, less likely to be taking lithium than were bipolar I patients. It seemed unlikely that these treatment differences accounted for the principal findings described here, however. Bipolar II patients were more, not less, likely to relapse and to manifest hypomania during follow-up than were nonbipolar patients, although bipolar II patients were more likely to be taking lithium. Moreover, although bipolar I patients were the most likely to be taking lithium, they were also the most likely to develop mania. It seems more probable, then, that group differences in treatment and the administration of effective treatment in general obscured differences that otherwise might have emerged.

To recapitulate, patients with bipolar I depression differed from those with nonbipolar depression in being more severely ill at baseline and more likely during follow-up to relapse, to make psychologically serious suicide attempts, and to experience both manic and hypomanic episodes. Patients with bipolar II depression differed from nonbipolar patients in the greater likelihood of relapse, multiple episodes, and hypomanic episodes during follow-up. Finally, when compared to patients with bipolar I depression, those with bipolar II depression were less severely ill at baseline, were much less likely to develop mania during follow-up, and had outcomes unaffected by the presence or absence of cycling before the follow-up period. Thus, bipolar II patients appeared to have no greater kinship with nonbipolar patients than they did with bipolar I patients. These results add additional support to the separation of bipolar I and bipolar II forms of affective disorder.

ACKNOWLEDGMENT

This study, from the NIMH Clinical Research Branch Collaborative Program on the Psychobiology of Depression: Clinical Studies, was conducted with the participation of the following investigators: G.L. Klerman, M.D. (Chairperson) (Boston); R.M.A. Hirschfeld, M.D. (Project Director and Co-Chairperson), and P. Griffith, Ph.D. (Washington, D.C.); M.B. Keller, M.D., and P. Lavori, Ph.D. (Boston); J.A. Fawcett, M.D., and W.A. Scheftner, M.D. (Chicago); N.C. Andreasen, M.D., W. Coryell, M.D., G. Winokur, M.D., and P. Wasek, B.A. (Iowa City); J. Endicott, Ph.D., P. McDonald-Scott, M.A., and J.E. Loth, M.S.W. (New York); and J. Rice, Ph.D., T. Reich, M.D., and D. Altis, B.A. (St. Louis). Other contributors include P.J. Clayton, M.D., M.M. Katz, Ph.D., E. Robins, M.D., R.W. Shapiro, M.D., and R. Spitzer, M.D.

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Ratings of Videotaped Simulated Patient Interviews and Four Other Methods of Evaluating a Psychiatry Clerkship

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Ratings of videotaped interviews with simulated patients were compared with four other measures commonly used to evaluate medical students during their psychiatry clerkship. Intercorrelations among self-reported attitude change, written examination grade, and student rating of satisfaction with the clerkship suggest that each measures different processes. Low but significant correlations between preceptor ratings of interaction skills and data-gathering skills and process and content scores based on an end-of-course videotaped interview suggest that preceptor ratings and the videotaped interview method evaluated the same skills. The authors conclude that preceptor evaluations supplemented by objective ratings of videotaped interviews show promise for evaluating the development of interviewing skills.

(Am J Psychiatry 1987; 144:316–322)

A 1984 study of a university medical practice clinic (1) reported that in only 23% of 74 office visits was the patient allowed to complete his or her opening statement of concern. On average, patients were interrupted 18 seconds after they began to speak; only one of the 52 interrupted statements was ever completed during the interview. Such findings suggest that flawed interviewing skills, including disinclination or inability to listen, may deprive physicians of important data and frustrate patients. Inadequate interviewing performance has been associated with patient dissatisfaction (2–5), noncompliance with prescribed treatments (6–9), doctor shopping, and even malpractice litigation (10–16).

Since the 1940s, American medical schools have offered courses in the psychosocial aspects of medicine and clinical interviewing (17–19). Departments of psychiatry carry the major responsibility for sensitizing students to the influence of psychological and social problems on health, illness, and recovery, although often without adequate support from the rest of the faculty. The importance of psychosocial issues and interviewing skills is widely recognized; however, few schools evaluate interviewing skills separately when grading students or when assessing the effectiveness of human behavior or psychiatry courses (20–23). This omission may reflect doubt on the part of educators that interviewing skills can be measured effectively or doubt that interviewing skills are as important as retention of course content. But if students are not evaluated for their ability to recognize and deal with emotional and psychosocial problems, then they and their teachers will remain uncertain about student mastery of this most important component of medical practice. Failure to evaluate this skill communicates that the faculty do not consider it important. Also, evaluating a course component only on the basis of student satisfaction trivializes it. Relying only on information retention aggravates the problem of overstressing cognitive content in the education of physicians.

Many techniques are now available to evaluate interpersonal skills directly and indirectly, including film or videotape examinations, paper and pencil examinations, patient management problems, computerized simulations, direct observation with generic or global rating scales, direct observation with data checklists, direct observation with interaction analysis, and conventional multiple-choice examinations (24–26).

According to Sanson-Fisher et al. (23), 46 studies published between 1970 and 1979 attempted to evaluate interviewing courses. Since the ultimate test of medical education is the clinical performance of a physician with a patient, one might expect preference for methods of evaluation capable of reproducing that criterion as closely as possible. Instead, methods that

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Supported by NIMH grant MH-15551.

Bryce Templeton, M.D., provided access to his scoring method for comparison. Charles M. Judd, Ph.D., and Donald Stilson, Ph.D., gave statistical consultation. Sam Silverstein, Ph.D., provided technical assistance and advice. Others contributing to this project included Donna Anderson, Ph.D., Naomi Miller, and Dava Golphenee.

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are easy to administer and score, irrespective of validity, appeared to be most widely employed (23, 27). The methods most frequently used to evaluate courses on psychosocial aspects of medical care do not measure change in target skills directly but rely on one or more of the following indirect measures of student learning that we have included for comparison in this study: 1) written examinations, 2) preceptor's or supervisor's subjective assessment of the student's progress, 3) attitude change as measured by before-and-after questionnaires, 4) the patient's satisfaction with the student's clinical skills, and 5) ratings of videotaped interviews with simulated patients.

Written examinations are easy to administer, and, as in the case of National Board of Medical Examiners examinations, the scores permit comparison between schools and departments. Ability to retain information is obviously important, but it has not been shown to predict clinical performance (28–41). Thus, the National Board has for more than a decade been conducting research on methods for assessing interviewing skills.

Evaluation of students' clinical performance by clinicians who have worked with them has the advantage of incorporating assessments of knowledge, skills, and personal qualities. But the validity and predictive power of preceptor assessments is unproven, and some evidence suggests that if the preceptor does not actually observe the student interviewing a patient, important information may be lost (27, 34, 36, 38–41).

Measuring change in attitude assumes that improved attitudes must improve clinical performance or that improved attitudes are a more easily measured concomitant of improvement in clinical skills. Neither rationale has been tested, nor is there empirical support from tests (42–53).

One study (53) reported a weak positive correlation between faculty assessments and patients' assessments of the clinical skills of the same students. Patients had been selected and trained by faculty to give a "reliable and coherent history" (53); thus, in a sense, they served as simulated patients.

The method of rating a student interviewing a real patient in an actual medical setting has incontestable face validity, but it also has drawbacks. Because of the variability and noncomparability of patients, any student's evaluation could be affected by the luck of the draw. Also, because of variable traffic through emergency rooms and outpatient clinics, the method is an inefficient use of an examiner's time.

Substituting a simulated patient for an actual one permits standardizing the medical problem and difficulty and enhances efficiency. The concern that one cannot learn anything from performance with simulated patients, although widespread, seems unwarranted. Performance with simulated patients has been shown to permit valid and objective evaluation of clinical performance (45–49) and to predict performance with actual patients (50).

The goal of this study was to compare several outcome measures commonly used to evaluate student performance in and effectiveness of a 6-week psychiatry clerkship. We wished to explore several questions: 1) Did students' attitudes toward the psychological and social aspects of medicine and clinical interviewing change from the beginning to the end of the clerkship? 2) Did interviewing skills improve, as measured by ratings of videotaped interviews with trained patient simulators? 3) Was there any relationship between changes in attitudes toward mental illness and changes in interviewing skills? and 4) Were there significant relationships between ratings of videotaped interviews and any of the other commonly used methods of evaluation used in medical education, such as attitude scores, preceptor grades, examination scores, or even students' satisfaction with the clerkship experience?

METHOD

For the purposes of this study, 10 "cases" were written by faculty members in psychiatry and family medicine. These cases described patients with histories and presenting complaints that represented those most often associated with psychological distress seen in a family medicine clinic. Experience with these constructed cases indicated that students found no substantial differences in difficulty among them. Seven men and women were employed to simulate these patients. Most of the simulators were professional actors or actresses. Each played more than one patient, and each patient was played by more than one simulator. Each patient-simulator combination was coached through several videotaped interviews and debriefed by a faculty member in psychiatry.

Our application of this method was designed to have a "low threshold"—to identify students who failed to reach a minimum level of competence in detecting and working with patients' psychosocial problems in the medical interviewing situation. Students who failed to meet the pass criterion were offered additional supervised experience and teaching.

Making fine discriminations throughout a wide range of abilities was not our purpose. Thus, it was not necessary to take into account such refinements as goodness of fit between style of interviewer and style of patient or to take account of the patient's response to the interviewer through interactional analysis.

A process scale measured the interviewer's skill; a content scale measured his or her information-gathering ability. The process scale focused on the behavior of the interviewer (51). Thirteen components (such as the use of open-ended questions and facilitating discussion of emotion-laden topics) were rated on a 5-point scale from 1 (unacceptable) to 5 (advanced); the process score was the summed item ratings. The maximum process scale score was 65 and the minimum was 13. The content scale was a case-specific checklist of symptoms and psychosocial data judged by faculty to be important for accurate assessment of

FIGURE 1. Sample Content Scale Checklist

RATING FORM FOR CONTENT
VIDEOTAPED SIMULATED PATIENT INTERVIEW

Site: _____ Date: _____
Doctor/Subject: _____ Patient/Simulator: _____
Rater: _____
Case: Headache 6

*Case History**

	Followed Up	Not Followed Up
I. *Social History*		
Marriage		
1. Former husband not interested in children	____	____
2. No (job) child support	____	____
Children		
3. 15-year-old boy does poorly in school	____	____
4. 12-year-old girl runs away from home	____	____
5. Crib death of fifth child	____	____
Job		
6. Lack of responsibility in job dissatisfying	____	____
7. Anxiety over losing job	____	____
8. Wants more education for upward mobility	____	____
Social networks		
9. One brother with drinking problem, needs support	____	____
10. Other siblings have health problems that cause worry	____	____
II. *Clinical*		
11. Weight gain last 6 months	____	____
12. Some unexplained crying	____	____
13. Wakens early, trouble with sleep	____	____
14. Considered suicide	____	____
15. Constipation	____	____
16. Tubal ligation	____	____
17. Alcohol, no	____	____
18. Cigarettes, no	____	____
19. Drug use	____	____
20. Energy level	____	____
III. *Treatment*		
21. Pills for headache	____	____

*For rater use in viewing videotape. Each item the doctor/subject elicits in the interview is checked.

If the information is used or followed up, place check mark in the first column. If the information is obtained but not used or followed up, put the check mark in the second column.

the patient's problems and for formulating a treatment plan (see figure 1). Its score reflects the percentage of content items the student elicited during the interview out of the total built into the case history. Since we had shown that neither practice nor patient variability affected the reliability or validity of these interview scores (51), we used a single videotaped interview at the beginning and another at the end of the clerkship to reflect student performance at those times.

The most desirable indicator of validity of these scores would be that they predicted level of skill in subsequent work with patients, perhaps even following graduation. Since such information was not available to us, we developed indirect indicators of the validity and reliability of these interview scores.

Indicators of Validity

1. In the absence of specific teaching of interviewing, students' interview scores did not improve on retesting after 6 weeks (51).

2. Mean interviewing scores of students were higher in medical schools that stressed teaching of human behavior and interviewing than in schools that gave less time and attention to these matters (54).

3. Discriminant validity and convergent validity for the scoring system were satisfactory (54).

4. Interview process scores discriminated among persons with known levels of proficiency. The mean score of 17 faculty members recognized as skilled interviewers was 50% higher than the mean score (34.9) of 261 fourth-year medical students.

5. Interview process scores correlated ($r=.48$, $p<.005$) with peer ratings of 20 students who had observed each other's work in clinical situations and were asked whether, in 10 years, they would be likely to refer a loved one to each classmate (54).

6. Students with high interview scores tended to report more satisfaction in their work with real patients than low-scoring students (54).

7. Interview scores predicted the responses of real patients who had been asked after the interview if they would be likely to follow the student physician's medical advice (54).

8. Students with below-passing scores who were provided additional teaching in interviewing subsequently improved their interviewing scores (55).

9. A series of videotaped interviews was rated by this method and also by the more comprehensive method that is part of the Interpersonal Skills Evaluation Project of the National Board of Medical Examiners (56). In a multiple regression using 13 interaction analysis items, we were able to predict 54% of the variance in our process scales and 56% of the variance in the content scores. No student who was graded as passing or failing by our method would have been reclassified by the use of the more refined method of interaction analysis designed specifically for evaluation of physician trainees. The National Board Skills Evaluation Project is capable of making much finer distinctions in interviewing skills than our pass, fail, or honors system.

Indicators of Reliability

1. Test-retest reliability of individual raters of 11 interviews was $r=.75$ ($p<.01$) after 9 months.

2. An interclass correlation of $r=.87$ ($p<.01$) was obtained by four raters rating the same interview independently.

Comparison of Five Methods of Evaluation

Seventy-two third-year medical students enrolled in one of four consecutive 6-week psychiatry clerkships in Colorado Psychiatric Hospital were the subjects. Students were assured that evaluations and information produced by the research team would not be available to other faculty and would not influence grading. Students gave consent to allow researchers access to their files and identified their otherwise

TABLE 1. Scores on Videotaped Interview and Attitude Scale of 72 Third-Year Medical Students Before and After 6-Week Psychiatry Clerkship

Measure	Score				t (df=142)	p
	Before Clerkship		After Clerkship			
	Mean	SD	Mean	SD		
Videotaped interview						
Process	45.22	5.79	47.16	5.94	3.34	.001
Content	52.55	16.49	57.93	16.36	1.66	.103
Attitude scale						
Social factors	32.35	4.43	33.10	4.26	2.19	.032
Doctor-patient relations	34.43	4.05	34.54	3.76	0.30	.768

anonymous evaluations of the clerkship as well as their examination scores, preceptor ratings, attitude change scores, and student satisfaction ratings. To assure anonymity, each student was assigned an identifying number. Raters of videotaped interviews were recruited off campus and especially trained for this project.

During the first 10 days of each clerkship and again during the last 10 days, each student was videotaped interviewing one of the seven randomly assigned patient simulators. No student interviewed the same simulator or encountered the same case twice. One of five raters, also randomly assigned, rated the videotapes to obtain the process and content scores.

After both the first and second videotaped interviews, each student filled out a questionnaire made up of two subscales of the Attitudes Toward Social Issues in Medicine Scale, developed by Parlow and Rothman (57). The social factors subscale from this questionnaire includes items that stress the importance of psychosocial elements in medical problems. The doctor-patient relations subscale consists of items that stress the relative importance of doctor-patient rapport compared with technical proficiency. Each subscale has nine items balanced to prevent response bias and scored from 1 (strongly agree) to 5 (strongly disagree).

At the end of the clerkship, the results of the routine psychiatry clerkship evaluations were obtained. Each preceptor rated each student using 6-point scales to evaluate data-gathering skills, interaction skills, and problem-solving skills. We also obtained the results of a 60-item multiple-choice end-of-clerkship examination as well as the questionnaire regarding students' satisfaction with the clerkship.

RESULTS

Table 1 displays the students' mean±SD interview ratings and attitude scale scores before and after the clerkship. Students improved in both aspects of interviewing, but only the improvement in interviewing skills (process) was significant. The students obtained higher scores on the social factors subscale of the attitude scale after the clerkship than before, but there was no change in scores on the doctor-patient relations subscale.

Table 2 displays the Pearson correlations among all of the pre- and postclerkship evaluation measures. The videotaped interview process and content scores were moderately correlated before the clerkship and somewhat more highly correlated afterward. There was a much lower correlation between the pre- and postclerkship process scores and no relationship between the pre- and postclerkship content scores. Pre- and postclerkship attitude scale scores were all moderately to highly correlated. The implication is that more change occurred in interviewing skills than in attitudes during the course of the clerkship. It is interesting that at the beginning of the clerkship there was a low but significant correlation between the two attitude scale scores and the interviewing process score. This relationship disappeared at the end of the clerkship. There was no relationship between the attitude scale scores and the interview content score either before or after the clerkship. Attitude scale scores are frequently relied on to evaluate human behavior courses; however, our study suggests that improvement in interview skills does not depend on attitude change as measured by the Attitudes Toward Social Issues in Medicine Scale.

Even though preceptors were asked to evaluate students' skill at interacting separately from problem-solving skill, their evaluations of students were highly intercorrelated. Predictably, preceptors' evaluations of students were moderately correlated with the satisfaction students expressed with the clerkship. Students who favorably impressed their preceptors were in turn more likely to express favorable impressions of these same preceptors and the clerkship. However, student satisfaction was not associated with retention of information as assessed in the final written examination. The absence of a relationship between student satisfaction and either written examination scores or interview skills as reflected in the videotape interview scores suggests caution about relying on satisfaction scores for course evaluation (58). In view of the frequency with which student satisfaction is used to stand for the success of courses, careful assessment of what student satisfaction relates to is in order (59). None of the interviewing scores was associated with the students' expressed satisfaction with the course.

Neither preceptor rating showed a relationship with either preclerkship interview score, but the postclerkship process score showed a low correlation with the

TABLE 2. Correlations (r) Among Videotaped Interview and Attitude Scale Scores Before and After 6-Week Psychiatry Clerkship and Preceptor Ratings, Written Final Examination Grades, and Student Satisfaction Ratings After Clerkship for 72 Third-Year Medical Students

	Interview Ratings				Attitude Scale Scores				Preceptor Ratings			Examination Grades	Student Satisfaction
	Before		After		Before		After						
Measure	1	2	3	4	5	6	7	8	9	10	11	12	13
Videotaped interview ratings													
Before clerkship													
1. Process	1.00												
2. Content	.55[a]	1.00											
After clerkship													
3. Process	.22[b]	−.01	1.00										
4. Content	.11	.11	.64[a]	1.00									
Attitude scale scores													
Before clerkship													
5. Social factors	.24[b]	.02	.06	.17	1.00								
6. Doctor-patient relations	.20[b]	−.05	.02	−.15	.51[a]	1.00							
After clerkship													
7. Social factors	.13	.04	.21[b]	.14	.80[a]	.41[a]	1.00						
8. Doctor-patient relations	.11	−.14	.03	−.02	.40[a]	.68[a]	.47[a]	1.00					
Preceptor ratings													
9. Data-gathering skills	.08	−.13	.12	.24[b]	.04	.16	−.03	.11	1.00				
10. Interaction skills	.16	−.06	.21[b]	.29[a]	−.05	.12	−.14	.04	.85[a]	1.00			
11. Problem-solving skills	.00	−.12	.13	.19	.06	.17	.01	.19	.83[a]	.86[a]	1.00		
12. Written examination grades	−.02	.14	.06	−.01	−.29[b]	−.16	−.15	−.08	.12	.07	.10	1.00	
13. Student satisfaction ratings	.03	−.19	.08	.21	.17	.23[b]	.23[b]	.27[b]	.40[a]	40[a]	.32[a]	.01	1.00

[a]p<.01.
[b]p<.05.

preceptor ratings of interaction skills. The postclerkship interview content score showed a low correlation with preceptor ratings of data-gathering skills and interaction skills.

DISCUSSION

Over the course of the 6-week psychiatry clerkship, the average interviewing process score improved significantly, although improvement in the average content score did not reach a conventional level of significance. It seems reasonable that interviewing technique would be more responsive to improvement through teaching and experience in a short time than would the ability to seek clinical and psychosocial information for case management. One of the two attitude scores also showed a significant improvement. However, the students who improved the most in interviewing skills were not the same students who registered the greatest gain in attitude scores. Positive attitudes, as indicated by questionnaire responses about the psychosocial aspects of medicine or the importance of doctor-patient rapport, do not necessarily assure good interviewing performance (60, 61). As Calnan and Rutter (62) reported, health beliefs only partially predict health behavior, and the reverse prediction can be equally true. Possibly, improved skills and behaviors of medical students could lead to changed attitudes, and positive attitudes could protect against future erosion of both the information and skills learned in interviewing courses (61). In one study (63), extraversion, self-confidence, and emotional awareness were seen as being associated with good clinical performance, and superior interviewing skills predicted good clinical performance.

Psychiatry clerkships typically rely on preceptor evaluations to grade student performance. It is noteworthy that even though preceptors in our study were asked to evaluate students' skills in data gathering, interaction, and problem solving separately, the high correlations among the evaluations of these skills suggest the operation of a halo effect. The failure to discriminate among important aspects of interviewing challenges the common practice of relying solely on preceptor impression or, for that matter, on any other single method to evaluate students or courses (64–67). It is especially interesting that preceptor ratings did not correlate at all with the interview scores that students obtained before the clerkship. The preceptor ratings of interaction skills, however, were significantly correlated with postclerkship interview process and content scores. Although the correlations were not high, the preceptors seemed to have been rating the same developing skills that were captured by interview scores.

The long-term predictive value of the five measures used in this study is unknown. One hopes that preceptors who evaluate students positively are responding to

qualities in students that they feel eventually lead to superior performance in a practicing physician. At the moment, evidence continues to suggest that the best predictor of future behavior is past and present behavior of the same kind (60) and that interviews of simulated patients can be used to assess broad levels of interviewing skills (49). Since psychiatric faculty consider interviewing a skill important enough to teach, they should consider it equally important to evaluate interviewing directly before attesting that the student is prepared to perform acceptably with the many patients who bring their psychological distress to medical settings.

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Dependent Personality Disorder Associated With Phobic Avoidance in Patients With Panic Disorder

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Eighty-eight panic disorder patients were divided into three groups according to the extent of their phobic avoidance (none, limited, or extensive). These groups were compared on three personality disorder instruments: the Structured Interview for DSM-III *Personality Disorders, the Personality Diagnostic Questionnaire, and the Millon Clinical Multiaxial Inventory. Phobic patients were found to have significantly more dependent personality disorder and* DSM-III *third-cluster personality disorders than nonphobic patients. A subgroup of patients with social phobic symptoms was found to resemble the rest of the phobic group in terms of personality.*
(Am J Psychiatry 1987; 144:323–326)

Clinicians have long suspected that patients with agoraphobia have more dependent personality traits than the average person. Andrews (1), for example, hypothesized that dependence on others was a major coping style of agoraphobic patients. Also, Shafar (2), using undefined ratings, concluded that dependence problems were present in 38% of her agoraphobic patients, and Buglass et al. (3), although reporting an overall negative study, found that 27% of their patients and none of their control subjects were aware of dependence about which they were resentful. Finally, Torgersen (4), in his study of monozygotic twins, found that the agoraphobic twin was most likely to be dependent. Researchers, however, have lacked the instruments and methodology to perform a definitive study.

Two developments have made it possible to examine with greater precision personality disorders in subgroups of patients with panic disorder. The first is that, unlike *DSM-III*, which separates panic and agoraphobic disorders, *DSM-III-R* (5) has brought them together and then made subdivisions (according to the extent of phobic avoidance) into uncomplicated panic disorder, panic disorder with limited phobic avoidance, and panic disorder with extensive phobic avoidance (agoraphobia). The second development is the introduction of standardized instruments for measuring *DSM-III* personality disorders (6). These two developments make it possible to compare the frequency of personality disorder in well delineated subgroups of patients with panic disorder by the use of standardized instruments for measuring personality. To our knowledge this is the first study to do so.

METHOD

Our sample consisted of the first 88 subjects admitted to a drug treatment study of panic disorder; they were volunteers recruited through the media. All were screened by the Structured Clinical Interview for DSM-III (7) and qualified for a diagnosis of panic disorder by *DSM-III-R* criteria. All gave informed consent. Volunteers were excluded from the study if they had organic brain syndrome, mental retardation, schizophrenia, or drug or alcohol abuse in the preceding year. Also excluded were volunteers who had symptoms of major depression that occurred before the onset of their anxiety disorder or that dominated the clinical picture. The clinical interview separated subjects with panic disorder according to *DSM-III-R* criteria into those without phobic avoidance (uncomplicated), those with limited phobic avoidance, and those with extensive

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Supported by NIMH grant MH-41055 and the Upjohn Company.
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phobic avoidance (agoraphobia). In addition, chart review identified a subgroup of subjects who had social phobic symptoms. These social phobic patients would have qualified for *DSM-III* social phobia except that they met the exclusion criterion of having spontaneous panic attacks. For convenience we refer to them as social phobic patients.

Personality tests were given to all subjects after they had been free of all antianxiety medication for at least 1 week. A trained interviewer administered the Structured Interview for DSM-III Personality Disorders (SIDP) (8) and gave the subjects the Personality Diagnostic Questionnaire (PDQ) (9) and Millon Clinical Multiaxial Inventory (10) self-report forms with instructions to complete and return them within 24 hours.

The SIDP is a semistructured 160-item interview covering all 11 *DSM-III* personality disorders. Interrater reliabilities (kappas) for joint interview are .71 for "any" personality disorder, .85 for borderline, .75 for histrionic, .62 for schizotypal, .45 for avoidant, and .90 for dependent (6). As recommended by the instrument's developer, significant others for all patients were also interviewed before personality disorder diagnoses were made. The time frame for the SIDP is the preceding 5 years, excluding periods of acute periodic emotional illness, such as major depression. Our raters were trained in part by one of the developers of the instrument (D. Stangl) (11).

The PDQ is a 152-item true/false measurement instrument covering all 11 *DSM-III* axis II personality disorders. Kappas for test-retest reliability at 1 month for a selected group of psychiatric patients with personality disorders were above .56 for paranoid, schizotypal, antisocial, borderline, avoidant, and compulsive disorders (12). The questionnaire was given according to the instructions of the developer of the instrument, which called for subjects to answer in relation to how they had been "over the past several years."

The Millon Clinical Multiaxial Inventory is a 175-item self-report instrument that generates numerical scales for the 11 *DSM-III* personality disorder diagnoses. Test-retest reliability at 4–6 weeks for a group of psychiatric patients ranged from .77 to .85 (10). The scales have good agreement with clinician-diagnosed *DSM-III* personality traits (6). The instrument was administered according to the developer's instructions; the time frame for it is the present.

The three subgroups of panic disorder patients (those with extensive phobic avoidance, limited phobic avoidance, and no phobic avoidance) were compared for any personality disorder, *DSM-III* personality disorder clusters, and individual personality disorders on the three tests. In addition, since there is evidence for poor agreement among these instruments (Reich et al., manuscript in preparation), we did an analysis using agreement on two of the three instruments as a requirement for the diagnosis of a personality disorder. Finally, the group of subjects with social phobic symptoms was compared on personality measures to the uncomplicated panic disorder group and the agoraphobic group.

TABLE 1. Frequency of *DSM-III* Personality Disorders According to the SIDP, the PDQ, and the Millon Clinical Multiaxial Inventory in 88 Patients With Panic Disorder[a]

Type of *DSM-III* Personality Disorder	SIDP (N=88)		PDQ (N=82)		Million Inventory (N=83)	
	N	%	N	%	N	%
First cluster	5	5.7	28	34.2	10	12.1
Schizoid	0	0	1	1.2	9	10.8
Paranoid	5	5.7	4	4.9	1	1.2
Schizotypal	0	0	28	34.2	1	1.2
Second cluster	13	14.8	22	26.8	23	27.7
Histrionic	9	10.2	14	17.1	10	12.1
Borderline	6	6.8	13	15.9	9	10.8
Antisocial	1	1.1	1	1.2	4	4.8
Narcissistic	0	0	1	1.2	5	6.0
Third cluster	31	35.2	31	37.8	45	54.2
Dependent	16	18.2	22	26.8	26	31.3
Avoidant	18	20.5	11	13.4	13	15.7
Compulsive	7	8.0	10	12.2	9	10.8
Passive-aggressive	2	2.3	1	1.2	20	24.1

[a]Not all measures were available for all patients.

RESULTS

There were 29, 23, and 36 patients in the uncomplicated panic, panic plus limited phobic avoidance, and agoraphobic groups, respectively. The numbers of women in these groups were 13 (44.8%), 14 (60.8%), and 25 (69.4%), respectively. These percentages were not significantly different, although there was a nonsignificant trend toward a larger proportion of women in the limited and extensive phobic avoidance groups. No intergroup statistical comparisons were significant. The subjects' mean±SD ages were 37.8±1.9, 35.9±2.1, and 39.5±1.7 years for the uncomplicated, limited phobic, and agoraphobic groups, respectively; these were also not significantly different. Although selected because they had a primary diagnosis of panic disorder, some subjects also had other disorders. On a lifetime basis, 21 (23.9%) had major depression and four (4.5%) had dysthymia.

For the entire panic disorder sample, the numbers of subjects who had no personality disorders were 50 (56.8%), 44 (53.6%), and 32 (38.6%) on the SIDP, the PDQ, and the Millon inventory, respectively. Table 1 shows the prevalence of *DSM-III* personality disorders according to each instrument. The most frequent axis II diagnosis was that of dependent personality disorder. Roughly a third of the subjects qualified for a *DSM-III* third-cluster personality disorder diagnosis. Table 2 demonstrates the frequency of dependent and third-cluster personality disorders for the three panic subgroups. For dependent personality disorder as measured by the PDQ, not only was the overall analysis significant, but uncomplicated panic was also signifi-

TABLE 2. Frequency of Dependent and *DSM-III* Third-Cluster Personality Disorders in Subgroups of Panic Disorder Patients According to the SIDP, the PDQ, and the Millon Clinical Multiaxial Inventory[a]

Diagnosis and Measure	Uncomplicated Panic Disorder (N=29) N	%	Limited Phobic Avoidance (N=23) N	%	Extensive Avoidance (Agoraphobia) (N=36) N	%	p (Fisher's exact test)
Dependent personality							
SIDP	2	6.9	6	26.1	8	22.2	n.s.
PDQ	2	7.4	8	38.1	12	35.3	.02
Millon inventory	3	11.1	9	42.9	14	40.0	.02
Consensus on two of the three tests	1	3.7	6	28.6	10	28.6	.03
DSM-III third cluster (anxious cluster)							
SIDP	7	24.1	11	47.8	13	36.1	n.s.
PDQ	6	22.2	11	52.4	14	41.2	n.s.
Millon inventory	9	33.3	15	71.4	21	60.0	.02
Consensus on two of the three tests	4	14.8	9	42.7	10	28.6	n.s.

[a]Not all tests were available for all subjects, so specific percentages may vary.

cantly different from both limited phobic avoidance (χ^2=5.1, df=1, p<.03) and extensive phobic avoidance (agoraphobia) (p=.01, Fisher's exact test). Similarly, for dependent personality as measured by the Millon inventory, uncomplicated panic disorder was significantly different from limited phobic avoidance (χ^2=4.8, df=1, p<.03) and extensive phobic avoidance (agoraphobia) (χ^2=5.0, df=1, p<.03). For dependent personality disorder as identified by consensus (two of the three instruments), there was a similar finding (uncomplicated panic disorder versus limited phobic avoidance, p=.03, Fisher's exact test; uncomplicated panic disorder versus agoraphobia, p=.02, Fisher's exact test).

Avoidant personality disorder as measured by the SIDP was less frequent in the uncomplicated panic disorder group than in the limited phobic avoidance group (three, or 10.3%, versus eight, or 34.8%; p=.04, Fisher's exact test). This finding is consistent with the significant differences between groups found for the *DSM-III* third cluster on the Millon inventory (see the third-cluster findings in table 2). Also consistent was the finding that for the consensus on the three measures, the third cluster was significantly less frequent in the uncomplicated panic group than in the limited phobic avoidance group (four, or 14.8%, versus nine, or 42.7%; p=.05, Fisher's exact test).

Eight subjects were identified as having significant social phobic symptoms. The number of women (three, or 37.5%) and the mean±SD age (39.3±3.6 years) of this group were not significantly different from the remaining uncomplicated panic subjects (11 women, or 45.8%, and 36.7±2.1 years). There was significantly more PDQ-defined schizotypal personality disorder in the social phobic group than in the uncomplicated panic group (six, or 75%, versus four, or 18.2%; p=.007, Fisher's exact test) and a similar surplus for avoidant personality disorder as measured by the SIDP (four, or 50%, versus two, or 8.3%; p=.02, Fisher's exact test). There were also significantly more social phobic subjects with *DSM-III* third-cluster disorders as defined by the Millon inventory (six, or 75%, versus five, or 22.7%; p=.03, Fisher's exact test) and as defined by the consensus measure of third-cluster disorders (four, or 50%, versus two, or 9.1%; p=.03, Fisher's exact test). The social phobic subjects did not differ in terms of personality disorders from the limited phobic avoidance and agoraphobic groups.

DISCUSSION

The purpose of this study was to determine whether the subdivisions of panic disorder could be validated by differences in the prevalence of *DSM-III* personality disorders when these disorders were measured in a standard fashion. We found that dependent personality disorders were more prevalent in the subgroups with phobic avoidance. Depending on the instrument used, roughly 40% of the subjects with some phobic avoidance met criteria for this personality disorder type. Because agoraphobia is a disabling symptom complex that responds to behavior therapy, the subcategorization of patients as agoraphobic appears meaningful. Our finding of an association with dependent personality supports the retention of this category in the nomenclature.

It is not clear from our findings whether the dependent personality disorder we observed was primary or secondary. The possibility that this disorder might be a predisposing condition for the development of agoraphobia in persons with panic disorder is a plausible one and is supported by the findings of Nystrom and Lyndegard (13). In a prospective study of more than 3,000 subjects, these authors found similar premorbid personality traits in persons who later developed anxiety disorders. Consequently, it is not unreasonable to believe that personality traits or disorders contribute to the development of an illness. It is even possible that personality disorders predispose to panic disorder itself.

Alternatively, it may be that personality disturbances are secondary to panic disorder, especially when complicated by phobic avoidance. Some patients

claim that before the onset of their phobic disorder they had been independent and self-confident, in contrast to the fearful clinging to a companion that later accompanied their illness. Their avoidant behavior and phobic cognitive style may well have contributed to an unwelcome dependence. In two cases that have been documented, patients without a previous history of personality pathology developed dependent personality and other traits and disorders (as measured by standardized instruments) after years of chronic panic disorder (Neenan et al., unpublished manuscript). Limitations in life style secondary to illness could also contribute to changes in cognition and temperament. Conceivably, both panic and dependence are epiphenomena of the same genetic process. Only prospective studies can answer the question of cause and effect.

There also appears to be support for a socially phobic panic disorder subgroup. Whether these patients should be classified with social phobic patients remains an unsettled question. In its most general form, social phobia is indistinguishable from avoidant personality disorder, so the association with avoidant personality disorder is not unexpected. It is interesting that our group had a high number of personality disorders from both the first and third *DSM-III* clusters—an unlikely combination (avoidant and schizoid personality disorders are mutually exclusive in *DSM-III*). Presumably, this group would require more support and special treatment measures to overcome their difficulties.

In sum, it appears that the distribution of *DSM-III* personality disorders supports the subdivisions of panic disorder proposed in *DSM-III-R*. The ultimate validity of this subgrouping, of course, awaits family, prospective, follow-up, and treatment studies.

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ECT-Induced EEG Asymmetry and Therapeutic Response in Melancholia: Relation to Treatment Electrode Placement

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Six right-unilateral and bilateral ECTs were equally effective in reducing Hamilton Rating Scale for Depression scores in 34 melancholic patients whose EEG symmetry did not change after ECT. However, a substantial therapeutic advantage was recorded for bilateral ECT in those patients whose EEG symmetry changed. Accentuation of ECT-induced EEG slowing over the right hemisphere was associated with right-unilateral ECT and a lesser treatment response, suggesting that the therapeutic advantage reported by some investigators for bilateral over right-unilateral ECT may be attributed to a poor outcome experienced by those unilateral ECT patients who developed right-sided EEG slowing.

(Am J Psychiatry 1987; 144:327–329)

The continuing controversy over the relative efficacy of unilateral and bilateral ECT in the treatment of depression is amply illustrated by the six most recent controlled double-blind studies: three found the methods equal (1–3) and three found an advantage for bilateral ECT (4–6). The explanation for these discrepant findings is not immediately apparent but may relate to the differential cerebral effects of the two methods (7). Several workers have reported hemispheric differences between bilateral and unilateral ECT on EEG measures (8). The availability of a data file containing numerically scored visual EEG analyses, computer-derived power spectral EEG analyses, and depression scale ratings in a sample of melancholic patients who had participated in a previous comparison of unilateral and bilateral ECT (4) provided the opportunity for us to examine whether the therapeutic advantage reported for bilateral ECT in that study was related to induced changes in cerebral electrical activity.

METHOD

The original sample consisted of 51 patients with melancholia who participated in a random-assignment, double-blind comparison of the therapeutic effects of unilateral and bilateral ECT (4). That study demonstrated a substantial and significant therapeutic advantage for bilateral ECT: patients receiving this treatment showed a mean improvement in Hamilton Rating Scale for Depression score of 81.1% after six ECTs, compared with a mean improvement of 55.5% for melancholic patients who received unilateral ECT ($t=2.85$, $df=47$, $p=.004$). We also attempted to obtain EEGs for all patients before and after their sixth ECT. Seventeen patients refused or were too agitated to participate; the remaining 34 patients (20 given unilateral and 14 given bilateral ECT) constitute the sample presented here.

The general project method was reported in detail elsewhere (4); only the EEG procedure is presented here. Fifteen-minute scalp-recorded EEGs were obtained with an eight-channel Grass polygraph (international 10–20 electrode system) on a day before the first ECT and 24 hours after the sixth ECT. These were read by an electroencephalographer (J.V.) who was blind to both treatment electrode placement and therapeutic response. All records were scored for the abundance, symmetry, and localization of background slowing and slow bursts (separately for theta and delta), spikes and sharp waves, and abnormal fast activity. Each record was also given a global abnormality score (1=none, 2=mild, 3=moderate, 4=marked, and 5=severe) and a global laterality score (1=left only, 2=left more than right, 3=symmetrical, 4=right more than left, and 5=right only). A symmetry change score was then obtained for these visually rated records by subtracting the post-ECT global laterality score from that obtained before treatment. This score could range from −3 (the maximum right-sided asymmetry) to 3 (the maximum left-sided asymmetry).

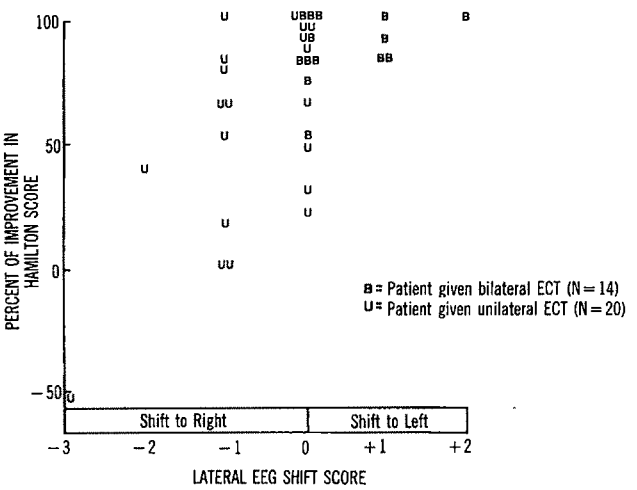
A subgroup of 15 patients (eight given bilateral and

Received Feb. 18, 1986; revised June 30, 1986; accepted Aug. 19, 1986. From the Department of Psychiatry and Behavioral Sciences, University of Health Sciences/Chicago Medical School; the Department of Psychiatry, New York University at Manhattan Psychiatric Center, New York; and the Nathan Kline Institute for Psychiatric Research, Orangeburg, N.Y. Address reprint requests to Dr. Abrams, Department of Psychiatry and Behavioral Sciences, University of Health Sciences/Chicago Medical School, 3333 Green Bay Rd., North Chicago, IL 60064.

Raymond Faber, M.D., collected some of the Hamilton depression scale data for this study.

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FIGURE 1. Relationship Between Visually Analyzed Lateral EEG Shift Scores and Improvement in Hamilton Depression Scale Scores of Patients Given Unilateral or Bilateral ECT



seven given unilateral ECT) also had EEGs recorded on magnetic tape for subsequent computer analysis. A 5-minute segment of artifact-free resting EEG was subjected to power spectral analysis by fast Fourier transform. The 0.5–3.5 Hz (delta) band width exhibited the maximum power increase after ECT, and right-to-left power ratios were calculated from the anterior temporal derivations, F8 and F7, each referenced against linked ears. A symmetry change score was then obtained for each patient by subtracting the F8-to-F7 ratio after the sixth ECT from that obtained at baseline. A negative score was associated with a relative or absolute delta power increase on the right, and a positive score was associated with a relative or absolute delta power increase on the left, analogous to the visually analyzed scores.

RESULTS

Visual EEG Analyses

The 34 patients (32 men and two women) ranged in age from 19 to 65 years (mean=49 years). Eighteen patients exhibited no ECT-induced change in EEG symmetry. For this group the mean percent of improvement in Hamilton depression scale score was only modestly greater for patients given bilateral (85.6%) than for those given unilateral (70.3%) ECT and failed to reach statistical significance ($t=1.35$, $df=16$, $p=.20$). However, for the 14 patients with an ECT-induced EEG symmetry change, there was a large and statistically significant therapeutic advantage for bilateral (92.0%) versus unilateral (40.5%) ECT ($t=2.45$, $df=17$, $p=.03$).

Figure 1 displays a scatter plot of the relationship between the percent of improvement in the Hamilton depression scale scores and visually analyzed EEG symmetry change scores, with the treatment electrode placements identified. Symmetry change scores ranged from −3 to 2, and percent of improvement scores ranged from 100% to −53%. Eleven patients (all given unilateral ECT) had an EEG accentuation on the right, and five (all given bilateral ECT) had an EEG accentuation on the left (Fisher's exact probability=.0002). The group given unilateral ECT contained the only study patient who got worse with treatment (a −53% change in Hamilton score). To avoid undue statistical influence of this outlying value, we analyzed the data by a median split of the percent of improvement scores: 10 of the 11 patients with a right-sided accentuation fell below the median, and four of the five patients with a left-sided accentuation fell above the median (Fisher's exact probability=.01).

TABLE 1. Relationship Between Improvement in Hamilton Depression Scores and Visual EEG Symmetry Scores of 34 Melancholic Patients Given Unilateral or Bilateral ECT

EEG Symmetry Score	Percent of Improvement in Hamilton Score	
	Mean	SD
−3 (N=1)	−53.0	0
−2 (N=1)	37.5	0
−1 (N=9)	51.1	36.9
0 (N=18)	77.9	24.6
1 (N=4)	89.4	7.6
2 (N=1)	100.0	0

Table 1 displays the mean percent of improvement scores for patients in each of the EEG symmetry change categories for all patients, revealing a systematic progression from a 53% worsening with a marked right-sided shift to a 100% improvement with a moderate left-sided shift ($F=5.6$, $df=5,28$, $p=.0028$). Combining the negative symmetry cells into a single group of 11 and the positive ones into a single group of five to eliminate the exaggerated effects of the single cases results in mean improvement scores of 40.5%, 77.9%, and 91.5% for the right-sided shift, no shift, and left-sided shift groups, respectively ($F=6.4$, $df=2,31$, $p=.0048$). Even when the single case cells (−3, −2, and 2) are omitted, an acceptable level of statistical significance remains ($F=3.8$, $df=2,28$, $p=.035$).

Nine of the 11 patients with right-sided asymmetry and four of the five patients with left-sided asymmetry were right-handed (n.s.). Information on drug therapy at the time of the post-ECT EEG was available for 22 patients: none of those with induced asymmetries had received psychotropic agents; all had received either nothing or nighttime sedation only. The mean age of patients with right-sided asymmetry was 51 years; for those with left-sided asymmetry it was 57 years (n.s.).

The most prevalent lateralized EEG abnormalities were theta and delta bursts and spike/sharp wave activity, all highly intercorrelated (e.g., the correlation [r] between spike/sharp wave activity and delta bursts was .9).

Computer EEG Analyses

The results of the computer EEG analysis in the subgroup of 15 patients augmented and clarified those obtained in the larger sample by visual analysis. The correlation between the ECT-induced change in the right-to-left delta power ratio and the percent of improvement in Hamilton scale score was significant ($r=.58$, $df=13$, $p<.001$); the outcome worsened as the EEG accentuation moved from left to right. (This analysis did not include the outlier in the unilateral ECT group because no computer EEG data were available for this patient.) Examining each treatment group separately revealed that for patients receiving unilateral ECT the correlation (r) between improvement and right-to-left power ratio shift was .908 ($df=13$, $p=.001$), but for patients given bilateral ECT it was only .102 (n.s.). These two correlation coefficients differed significantly from each other ($p<.05$, two-tailed).

We considered the possibility that patients with right-sided EEG accentuation might have experienced cognitive changes associated with dysphoria and a poor ECT response. In another part of the same study from which the present sample derives (4) we had collected neuropsychological test data on 37 patients before and after six ECTs in order to study the cognitive effects of ECT (9). Of the 34 patients in the visual EEG analysis portion of the present study, 32 had also received cognitive testing, as had all 15 patients in the computer EEG subgroup. The correlations between global cognitive impairment score and either visually or computer-analyzed lateral EEG change were both insignificant ($r=.11$, $df=30$, and $r=.16$, $df=13$, respectively; $p=.28$ in both instances).

We also examined individual Hamilton scale items for their relation to ECT-induced changes in the F8-to-F7 power ratio. Of 15 items tested, only early morning waking exhibited a significant correlation ($r=-.75$, $df=13$, $p=.001$), probably within chance expectations for the number of separate statistical tests performed.

DISCUSSION

This study confirms and extends our previous report (10), which was the first to determine that bilateral ECT and nondominant unilateral ECT had opposite effects on visually rated EEG lateralization. We reported that 28 of 29 patients with left-sided accentuation of post-ECT slowing had received bilateral ECT and that 21 of 26 patients with right-sided accentuation had received unilateral ECT (exact probability $=10^{-9}$). Although a power-spectral EEG analysis of a subset of those patients (11) confirmed the visual observations, no relation was found between ECT-induced left- or right-sided EEG slowing and improvement in depression. However, no attempt was made to examine right-to-left power ratios in relation to treatment response.

Interpretation of the present finding of a strong relation between ECT-induced lateral EEG asymmetry and treatment response in melancholia as an explanation of the differential efficacy of unilateral and bilateral ECT is confounded not only by the fact that bilateral ECT was generally more effective than unilateral ECT but also by the fact that all left-sided changes occurred with bilateral ECT and all right-sided ones with unilateral ECT. However, there is an indication of a closer link between improvement and induced EEG asymmetry within the unilateral group alone: the computer-analyzed data show a strong graded effect of increasing right-sided accentuation and a poor outcome; the small size of this subsample ($N=8$) precludes any stronger interpretation of this finding.

Whether a lateral EEG change predicts outcome with ECT regardless of treatment electrode placement or just in patients receiving unilateral ECT cannot be determined from the present study. These questions can be resolved only by a controlled comparison of the therapeutic and EEG effects of left- versus right-sided unilateral ECT.

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High Rate of Affective Disorders in Probands With Attention Deficit Disorder and in Their Relatives: A Controlled Family Study

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In a controlled family study of attention deficit disorder, data were collected on first-degree relatives of 22 children with attention deficit disorder and 20 normal children. The rate of major affective disorder was significantly higher in the attention deficit disorder probands (32%) and their relatives (27%) than in the normal control subjects (0%) and their relatives (6%). The findings indicate that attention deficit disorder is associated with higher risk for affective disorder and suggest that probands who have both disorders may represent a distinct subgroup.

(Am J Psychiatry 1987; 144:330–333)

Attention deficit disorder is a chronic, heterogeneous disorder of unclear etiology that affects 3%–5% of school-age children (1). Depressive symptoms have been associated with this disorder (2), and symptoms of distractibility, impulsivity, hyperactivity, and emotional lability are commonly encountered and appear to bear some similarities to features of bipolar disorder, manic. It is possible that some children affected with either disorder are misdiagnosed and that some children have both disorders. Family studies based on structured interviews are a useful approach to help clarify issues of comorbidity (3, 4). Structured interviews are more likely than the standard clinical assessment to help ascertain multiple diagnostic categories in a subject (5).

Presented at the annual meeting of the Society of Biological Psychiatry, Washington, D.C., May 7–11, 1986. Received Feb. 5, 1986; revised July 14, 1986; accepted Aug. 19, 1986. From the Pediatric Psychopharmacology Unit, Massachusetts General Hospital; and Harvard Medical School Program in Psychiatric Epidemiology. Address reprint requests to Dr. Biederman, Pediatric Psychopharmacology Unit, Massachusetts General Hospital, ACC-625, Boston, MA 02114.

Supported in part by grants from the Charlupski Foundation and the Milton Fund to Dr. Biederman.

The authors thank Michael S. Jellinek, M.D., Ronald Benz, M.D., Ross Baldessarini, M.D., and Steven Faraone, Ph.D., for their help.

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In a recent family prevalence study, we reported high rates of major affective disorders in attention deficit disorder probands and in their first-degree relatives, compared with relatives of normal control subjects (6). The purpose of the current analysis was to evaluate further the association between attention deficit disorder and affective disorders. We hypothesized that the rate of affective disorders would be higher in relatives of attention deficit disorder probands who had a concomitant major affective disorder than in relatives of attention deficit disorder probands who did not have an affective disorder. To our knowledge, this was the first comprehensive study to investigate the frequency and types of psychopathology in first-degree relatives of children who had attention deficit disorder and an associated diagnosis of a major affective disorder.

METHOD

All subjects were Caucasian, non-Hispanic boys who came from the same geographical area and outpatient hospital setting. The sample consisted of 22 consecutive patients with attention deficit disorder referred to the Pediatric Psychopharmacology Unit and the Child Psychiatry Service at the Massachusetts General Hospital. These probands were boys 6–17 years old with a full scale IQ higher than 80 on the Wechsler Intelligence Scale for Children who met *DSM-III* criteria for attention deficit disorder, with the disorder manifested in at least two settings (school, home, or clinic). Excluded from the study were adopted, autistic, and psychotic children. In all cases attention deficit disorder was considered the primary diagnosis.

The normal comparison group consisted of 20 nonadopted, healthy boys, 6–17 years of age, whose socioeconomic status (Hollingshead two-factor index) was comparable to that of the attention deficit disorder subjects. They were selected from the pediatric primary care service at the Massachusetts General Hospital and screened for absence of medical and psychi-

atric disorders. All parents gave written consent for participation in the study.

We studied only biological relatives and full siblings. Raters were blind with respect to the clinical status of the probands; psychiatric assessments of the probands and their siblings were based on indirect interviews with the mothers in which we used the Diagnostic Interview for Children and Adolescents-Parent Version (7). Diagnostic assessments of parents were based on direct interviews with both parents in which we used the National Institute of Mental Health Diagnostic Interview Schedule (8) to cover adult disorders and an addendum based on the Diagnostic Interview for Children and Adolescents to cover childhood disorders.

Diagnostic hierarchies were suspended, and for every subject all possible diagnoses were made. Diagnoses were not mutually exclusive and represented lifetime rates. We calculated morbidity risk by the Weinberg short method of age correction (9). Age of risk for affective disorders was 6–60 years; for other disorders it was determined according to *DSM-III* guidelines, as described elsewhere (6).

Power tables (10) show that 70 relatives per group was sufficient to detect differences of 15% (or more) with a power of 80% in the rates of affective disorders among relatives of attention deficit disorder probands versus the relatives of the control group, considering that the rate of affective disorders in the latter group was between 5% and 10%. We analyzed the data by using the chi-square approximation with Yates' continuity correction from the 2×2 contingency tables. All tests of statistical significance were two-tailed and set at the .05 level.

RESULTS

The attention deficit disorder probands were similar to the normal control subjects in age (mean±SD= 11.1±0.7 versus 10.4±0.6 years), age of parents (mean±SD=38.4±0.9 versus 37.7±0.8 years), age of siblings (mean±SD=11.9±0.9 versus 10.8±0.1 years), sibship size (mean±SD=1.5±0.2 versus 1.6± 0.2), social class (class I=14% versus 5%, class II=18% versus 10%, class III=18% versus 50%, class IV=32% versus 30%, class V=18% versus 5%), and proportion of intact families (64% versus 85%). All mothers in both groups were interviewed. A minority of fathers in both groups could not be directly interviewed, and in those cases information was gathered from their wives. A similar proportion of unavailable fathers was found in the attention deficit disorder group and the normal comparison group (18% versus 30%).

Compared with relatives of the normal control subjects, relatives of the attention deficit disorder probands had higher rates of affective disorders (N=13, morbid risk=31%, versus N=2, morbid risk=6%; p<.05). These disorders consisted of nonbipolar major depression (N=11 [seven mothers, two brothers, and two sisters], morbid risk=27%, versus N=2 [one mother, one father], morbid risk=6%; p<.05) and dysthymic disorder (N=2 [two fathers], morbid risk=6%, versus N=0; n.s.). No relative in either group had bipolar disorder. The computed odds ratio for major depressive disorder was calculated to be 5.0 (confidence interval=1.2–20.9), taking into account only relatives with definite nonbipolar major depression.

Seven (32%) of the attention deficit disorder probands received a lifetime diagnosis of a major affective disorder and 15 (68%) did not. This rate of major affective disorder was significantly higher than the rate for the normal control subjects (N=0; p<.05). Five (23%) of the attention deficit disorder probands received a lifetime diagnosis of nonbipolar major depression, and two (9%) received a lifetime diagnosis of bipolar disorder. In all cases the onset of attention deficit disorder preceded the onset of the affective disorder by at least 1 year. The probands with attention deficit disorder who had major affective disorder also had learning disabilities and were receiving remedial help.

The rates of attention deficit disorder and other disorders were similar in the relatives of probands who had a lifetime diagnosis of major affective disorder and those who did not. Although not statistically significant, the rate of major depression was higher in relatives of attention deficit disorder probands without a major affective disorder than in relatives of attention deficit disorder probands with a major affective disorder (N=9 [five mothers, two brothers, and two sisters], morbid risk=30%, versus N=2 [two mothers], morbid risk=18%; n.s.).

Relatives of both attention deficit disorder subgroups differed significantly in their rate of attention deficit disorder compared with the rate in relatives of normal control subjects. Relatives of probands with attention deficit disorder and no affective disorders differed from relatives of normal control subjects in rates of oppositional disorder and major depression, while relatives of attention deficit disorder probands who had major affective disorders differed from relatives of control subjects in rates of separation anxiety disorder, antisocial personality disorder, obsessive-compulsive disorder, oppositional disorder, and drug dependence (table 1).

DISCUSSION

Contrary to our expectations, we were unable to show that affective disorders aggregated in the pedigrees of probands with a concomitant affective disorder. The diagnosis of a major affective disorder in the subgroup of attention deficit disorder probands was not associated with a lower familial risk for attention deficit disorder or a higher risk for affective disorders, as one might have expected with probands having only affective disorders (11, 12). This suggests that atten-

TABLE 1. Morbid Risk of *DSM-III* Psychiatric Disorders in First-Degree Relatives of Attention Deficit Disorder Probands With and Without Major Affective Disorders and in Relatives of Normal Control Subjects

Diagnosis	Relatives of 7 Attention Deficit Disorder Probands With Major Affective Disorder (N=22)			Relatives of 15 Attention Deficit Disorder Probands Without Major Affective Disorder (N=53)			Relatives of 20 Normal Control Subjects (N=73)		
	Number		Morbid	Number		Morbid	Number		Morbid
	Ill	At Risk	Risk (%)	Ill	At Risk	Risk (%)	Ill	At Risk	Risk (%)
Affective disorders									
Any affective disorder	3	11	27	10	31	32[a]	2	35	6
Major depression	2	11	18	9	30	30[a]	2	35	6
Dysthymic disorder	1	10	10	1	26	4	0	34	0
Bipolar disorder	0	10	0	0	26	0	0	34	0
Anxiety disorders									
Separation anxiety	3	19	16[a]	1	47	2	1	60	2
Overanxious disorder	2	18	11	9	47	19	5	60	8
Agoraphobia	1	12	9	2	21	10	1	35	3
Simple/social phobia	1	12	8	3	27	11	1	35	3
Obsessive-compulsive disorder	2	11	18[b]	1	26	4	0	34	0
Behavioral disorders									
Attention deficit disorder	6	21	29[c]	18	52	35[d]	4	70	6
Conduct disorder	0	18	0	3	48	6	0	60	0
Oppositional disorder	4	19	21[b]	15	49	31[c]	3	60	5
Antisocial personality disorder	3	14	21[a]	1	34	3	1	43	2
Substance use disorders									
Any substance use disorder	4	9	44	9	24	38	7	27	26
Alcohol abuse	1	8	13	3	21	14	4	25	16
Alcohol dependence	1	8	13	4	21	19	2	24	8
Drug abuse	0	7	0	1	20	5	2	24	8
Drug dependence	2	8	25[b]	3	21	14	0	23	0
Developmental disorders									
Enuresis	4	19	21	8	46	17	8	60	13
Encopresis	1	18	6	3	47	6	0	68	0
Tics (non-Tourette)	1	18	6	2	47	4	1	59	2
Sleep walking/terrors	2	17	12	5	46	11	4	60	7
Language disorder/stuttering	1	18	6	1	47	2	3	61	5

[a]Significant difference from control group ($p<.05$).
[b]Difference from control group ($p<.10$).
[c]Significant difference from control group ($p<.01$).
[d]Significant difference from control group ($p<.001$).

tion deficit disorder probands who have a major affective disorder and those who do not may be genotypically similar with regard to the predisposition for major depression. These data are too preliminary to support inferences about the mechanisms underlying the familial coaggregation of attention deficit disorder and major depression. However, the results do not appear to be consistent with the multifactorial polygenic hypothesis in which attention deficit disorder with major affective disorder would require the presence of more familial etiological factors than attention deficit disorder without it. The similar rates of major depression and attention deficit disorder among the two types of attention deficit disorder probands are more consistent with the hypothesis that a sporadic environmental effect is responsible for differences in the rate of major affective disorder among attention deficit disorder probands (13).

Relatives of attention deficit disorder probands with major affective disorder had higher rates of anxiety disorders, antisocial personality disorder, and drug dependence than did relatives of normal control subjects. A higher rate of anxiety disorders is consistent with findings of higher rates of anxiety disorders in relatives of adult probands with affective disorders (3). A higher rate of antisocial personality in relatives of attention deficit disorder probands with major affective disorder is consistent with findings reported by Puig-Antich (14) of high rates of conduct disorder in prepubertal children with affective disorder. High rates of sociopathy (antisocial personality disorder) and alcoholism in fathers of probands with hyperactive child syndrome (attention deficit disorder) have been reported in previous family studies (15–19). Although the overall rates of antisocial personality and substance use disorders did not differ between relatives of attention deficit disorder probands and relatives of normal control subjects (6), relatives of the subgroup with a concomitant major affective disorder had a higher risk of these disorders. The nature of the association between attention deficit disorder, affective disorders, anxiety disorders, antisocial personality, and substance use disorders is unknown and requires further investigation.

It is unclear whether affective symptoms associated with attention deficit disorder are related to attention

deficit disorder itself or to the coexistence of two disorders. Depressive symptoms and moodiness have been associated with attention deficit disorder (2). The finding of manic symptoms in attention deficit disorder patients is complex. The signs and symptoms of mania are difficult to identify in children (11), and there are difficulties in establishing boundaries between manic and attention deficit disorder symptoms. However, the availability of operational criteria for affective disorders and of structured interviews to help elicit them increases the likelihood of making those diagnoses by reducing variance in information and criteria (20). Thus, our finding of major affective disorder on the basis of blind structured interviews in a subgroup of attention deficit disorder probands in which the major affective disorder followed the onset of attention deficit disorder, suggest that this group of children may have both attention deficit disorder and a major affective disorder. Moreover, attention deficit disorder probands with a major affective disorder also had learning disabilities, which are a frequent concomitant of attention deficit disorder (21) and not of affective disorders.

The findings reported in this study should be viewed against their methodologic limitations. First, although power analysis indicated that we had sufficient power to detect overall differences between the rates of affective disorders in relatives of attention deficit disorder probands and the rates in relatives of normal control subjects, we did not have adequate power after the division of attention deficit disorder probands into those with and those without a major affective disorder to fully test the aggregation of major affective disorders in the relatives of the two attention deficit disorder subgroups. Nevertheless, we were able to show significant differences in the rate of major depression between relatives of probands without major affective disorder and relatives of control subjects but not between control relatives and relatives of the subgroup with major affective disorder. Second, although the difference in distribution of socioeconomic status between attention deficit disorder and normal control families was not statistically significant, normal control families had a higher frequency of class III, which may have biased our sample.

In conclusion, the observation that attention deficit disorder is associated with a higher risk for affective disorders in probands and relatives calls for further studies with larger sample sizes. Such studies may help determine whether attention deficit disorder probands with a concomitant affective disorder represent a meaningful subgroup.

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5-Hydroxytryptophan-Induced Cortisol Response and CSF 5-HIAA in Depressed Patients

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To determine if the enhanced cortisol response to oral administration of the serotonin (5-HT) precursor 5-hydroxytryptophan (5-HTP) that has been reported in unmedicated depressed and manic patients might be related to brain monoaminergic metabolism, the authors assessed correlations between 5-HTP-induced cortisol response and CSF in nine depressed patients. They found a significant negative correlation with CSF levels of 5-hydroxyindoleacetic acid, a 5-HT metabolite, but not with CSF levels of other monoamine metabolites. This finding is consistent with the hypothesis that low presynaptic brain serotonergic activity may be related to enhanced cortisol response to 5-HTP in depressed patients.

(Am J Psychiatry 1987; 144:334–337)

The serum cortisol response to 5-hydroxytryptophan (5-HTP), a precursor of serotonin (5-HT), has been reported to be enhanced in unmedicated depressed and manic patients (1). Heightened 5-HT receptor sensitivity, possibly secondary to diminished presynaptic serotonergic activity, was postulated as the cause of this enhanced cortisol response to 5-HTP (1). It has been demonstrated that diminished presynaptic serotonergic activity due to lesions of the raphe neurons or interference with 5-HT synthesis by *p*-chlorophenylalanine enhances the corticosterone response to 5-HTP or 5-HT agonists (2 and unpublished observations of Meltzer et al.). Low presynaptic serotonergic activity has been presumed to occur in depressed patients on the basis of diminished CSF concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT (3,4); however, not all studies have found low CSF 5-HIAA levels in depression (3–6).

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Supported in part by grants MH-41684, MH-41683, and MH-41594, training grant MH-14651 (Dr. Lowy), and Research Career Scientist Award MH-47808 (Dr. Meltzer) and by the Cleveland Foundation.

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We postulated that CSF 5-HIAA levels would be negatively correlated with the 5-HTP-induced increase in cortisol in depressed patients if both were, in fact, related to diminished presynaptic serotonergic activity. To determine the specificity of the relationship between CSF 5-HIAA and cortisol response to 5-HTP, we also measured the CSF levels of the major metabolites of other biogenic amines, i.e., norepinephrine and dopamine, which might influence the activity of the hypothalamic-pituitary-adrenal (HPA) axis: 3-methoxy-4-hydroxyphenylglycol (MHPG), 3,4-dihydroxyphenylacetic acid (DOPAC), and homovanillac acid (HVA).

METHOD

Nine patients admitted voluntarily to the inpatient research unit of the Laboratory of Biological Psychiatry of the University of Chicago gave written informed consent to participate in this study. All were in good health, had no organic psychotic symptoms, and had no recent history of alcohol or other drug abuse. All patients completed the Hamilton Rating Scale for Depression (7) within 1 week of admission; they also completed the Schedule for Affective Disorders and Schizophrenia (8). Two psychiatrists and one psychologist, who were unaware of the laboratory data obtained on the patients, used the Research Diagnostic Criteria (9) and all other available information to determine, by consensus at discharge, each patient's diagnosis: six patients had major depression, and three had schizoaffective disorder, mainly affective. All nine patients met *DSM-III* criteria for major depression or bipolar depression, with or without mood-incongruent delusions. Six of the nine patients were men and three were women; their mean±SD age was 32.2±10.5 years. All nine patients were drug free for a minimum of 1 week (mean±SD=11.15±5.5 days) after admission to the research unit.

We carried out the 5-HTP challenge study as previously described (1), using a 200-mg oral dose of D,L-5-HTP. For 3 hours after and 30 minutes before the patients ingested 5-HTP, an indwelling intravenous catheter was inserted to obtain serum for determining cortisol levels. CSF samples were obtained 3–5 days before the patients ingested 5-HTP. A lumbar puncture was performed at 9 a.m., with each patient in a fasting

TABLE 1. CSF Monoamine Metabolite Concentrations and Correlations With Maximum 5-HTP-Induced Cortisol Response for Nine Depressed Patients

Metabolite	CSF Levels (mg/ml) Mean	SD	Correlation With Δ Serum Cortisol (rho)
5-HIAA	12.2	10.2	−.65[a]
HVA	34.6	13.5	−.46
DOPAC	2.7	2.1	.21
MHPG	7.2	2.4	.43

[a]p=.05.

state. All lumbar punctures were nontraumatic, and the CSF was free of blood; approximately 10 ml of CSF were withdrawn and stored at −70° C until analyzed. To assess the relationship between the CSF concentrations of monoamine metabolites and the cortisol response to 5-HTP, we correlated peak minus baseline serum cortisol values with CSF levels of MHPG, DOPAC, HVA, and 5-HIAA. Cortisol levels were determined by radioimmunoassay (1).

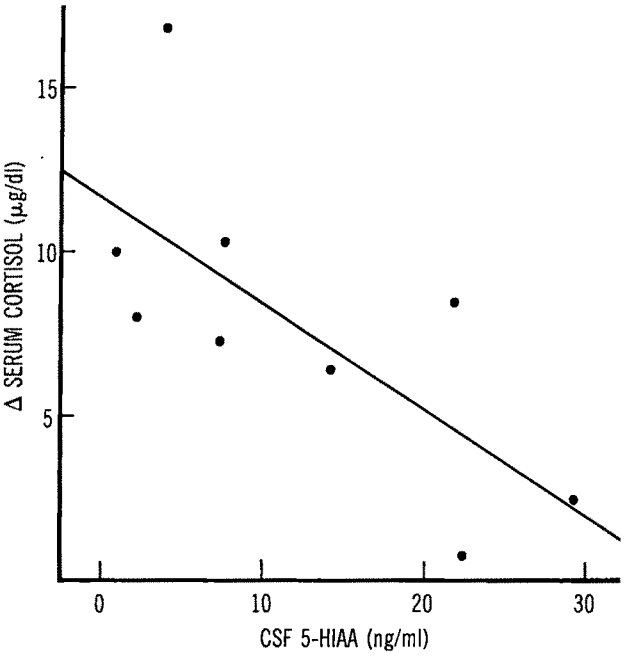
For measurements of CSF levels of monoamine metabolites, two high-performance liquid chromatography methods with electrochemical detection, recently developed by Koyama et al. (10), were used. Briefly, after precipitation of proteins with perchloric acid, the supernatant was stored on ice until injection into the chromatograph. The mobile phase for the simultaneous assay of 5-HIAA, DOPAC, and HVA consisted of 0.1 M sodium acetate containing 250 mg/liter of EDTA and 7% methanol, pH 4.5. The mobile phase for the MHPG assay was 0.1 M monochloracetic acid with 30 mg/liter of sodium octyl sulphate and 250 mg/liter of EDTA, pH 3.0. The instrument consisted of a Bioanalytical System (BAS) LC-304 solvent delivery system; a 4.5×250 mm Ultrasphere ion pair (5 μ particle size) analytical column, and a BAS LC-4A electrochemical detector. The detector flow cell had a BAS TL-3 glassy carbon working and an Ag/AgCl reference electrode. All separations were achieved isocratically at 27° C with a flow rate of 1.2 ml/minute. The flow cell potential was maintained at 0.75 V versus Ag/AgCl, and detector sensitivity was usually set at 5 nA full-scale. These procedures had an average intra-assay coefficient of less than 2.3% and an interassay coefficient of less than 6.5% for each substance.

Correlation coefficients (rho) were determined by the method of Spearman.

RESULTS

The mean±SD CSF concentrations of the major monoamine metabolites for all nine depressed patients are presented in table 1. The CSF concentration of 5-HIAA (12.2±10.2 ng/ml) in the depressed patients was low compared to published data on normal control subjects, a finding consistent with the results of some, but not all, studies of CSF 5-HIAA in depression (3, 4). There were no significant correlations between the CSF concentrations of the four metabolites, although the concentrations of 5-HIAA and HVA approached a significant positive correlation (rho=.54, p=.15), as has frequently been reported previously (3, 4).

FIGURE 1. Maximum Serum Cortisol Response and CSF Concentration of 5-HIAA in Nine Depressed Patients



The mean±SD serum cortisol response for all depressed patients was 7.8±4.5 μg/dl, similar to the value obtained in our larger study (1). We found a significant negative correlation between the maximum serum cortisol response to 5-HTP (Δ serum cortisol) and CSF 5-HIAA levels only (rho=−.65, p=.05) (figure 1).

There was no correlation between age and the concentration of CSF 5-HIAA or serum cortisol. The fact that two of the three women had CSF 5-HIAA levels that were among the highest we found is consistent with previous reports of increased 5-HIAA in women (6), but one of the women had a low cortisol response and the other had a cortisol response above the median. We found no gender differences in the cortisol response to 5-HTP in this or our larger study (1). The correlations between basal serum cortisol and concentration of CSF 5-HIAA or cortisol response were not significant. CSF 5-HIAA levels did not correlate with Hamilton depression scale suicide ratings.

DISCUSSION

In this study, we examined the relationship between the increase in serum cortisol in response to a low dose of 5-HTP given orally to depressed patients and the

CSF concentration of several monoamine metabolites. Despite the relatively small number of subjects, a significant negative correlation emerged between the increase in serum cortisol levels after 5-HTP ingestion and the CSF level of 5-HIAA, the major metabolite of 5-HT.

The Δ cortisol observed in our nine depressed patients was similar to that previously reported in a larger sample of depressed patients and greater than that of normal control subjects (1). We combined data from patients with an RDC diagnosis of schizoaffective depression, mainly affective, with data from patients with major depression because no differences in the cortisol response to 5-HTP had been found between these two diagnostic groups in a larger series (H.Y. Meltzer, unpublished data). Furthermore, the RDC schizoaffective depressed patients, mainly affective, met *DSM-III* criteria for major depression with mood-incongruent delusions.

The levels of CSF 5-HIAA reported here are comparable to the levels reported in some studies of depressed patients (3, 4, 6, 11, 12), whereas others have reported mean levels several times higher (3, 4, 13, 14). Assay differences as well as loss during storage may account for variability between studies. CSF from normal control subjects was not available to us. The reliability of our assay was satisfactory in the range of 1–30 ng/ml. The correlation between HVA and 5-HIAA CSF levels observed here is indirect evidence for the relative reliability of both assays, since this correlation has been observed in most previous studies of CSF metabolites of depressed patients (15, 16). No relationship between CSF 5-HIAA levels and Hamilton depression scale suicide ratings was present in this small sample. Probenecid has been used to block the egress of acid metabolites from CSF, thus permitting an estimation of the rate at which the metabolites are transported into the CSF (16, 17), but the validity of this as a measure of neurotransmitter turnover appears suspect (18). No corrections for sex, height, or age effects on 5-HIAA were made in this small sample. The correction for age and sex is very small in depressed patients (12). No relationship between sex and the 5-HTP-induced increase in serum cortisol has been found (1). The negative correlation between CSF 5-HIAA and Δ cortisol, together with the lack of correlation between CSF MHPG, DOPAC, or HVA and Δ cortisol, suggests that the cortisol response to 5-HTP is mainly influenced by the serotonergic system. We also have found no significant correlation between CSF 5-HIAA and platelet monoamine oxidase activity (Meltzer et al., unpublished data).

The enhanced cortisol response to 5-HTP in depressed patients could be due to a variety of factors affecting the absorption and metabolism of 5-HTP or 5-HT, to the ability of 5-HT to stimulate the HPA axis, or to differences in the intrinsic activity of the HPA axis itself (1). The fact that we have found no significant differences between depressed patients and control subjects in serum 5-HTP or 5-HIAA levels after 5-HTP ingestion (10) suggests that the difference in cortisol response between the depressed patients and normal control subjects is not due to pharmacokinetic factors. This leaves open the possibility that differences in CNS metabolism of 5-HT (e.g., release, reuptake, deamination) or 5-HT receptor changes may be the most important determinants of the cortisol response to exogenous 5-HTP. The positive correlation of CSF 5-HIAA concentration with 5-HIAA levels in human postmortem cerebral cortex (19) suggests that CSF measures reflect at least some aspects of brain 5-HT metabolism. The finding of low levels of CSF 5-HIAA observed in this depressed sample is consistent with a reported increase in numbers of 5-HT_2 receptors in the brain observed in one study of depressed patients (20), but not replicated in another (21), and in turn with an enhanced cortisol response to 5-HTP, which studies in rats suggest may be mediated by 5-HT_2 receptors (22). We have tested this hypothesis more directly by comparing the cortisol response to 5-HTP with the cortisol response to a direct acting 5-HT agonist, MK 212, and found a highly significant correlation (Meltzer et al., unpublished data).

The results of this study suggest that peripheral measures, i.e., the 5-HTP-induced increase in cortisol, provide further evidence of altered central serotonergic activity in depression.

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Prediction of Response to Nortriptyline and Phenelzine by Platelet MAO Activity

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Thirty-seven depressed patients over the age of 55 were treated for 5–7 weeks with either nortriptyline, a tricyclic antidepressant, or phenelzine, a monoamine oxidase (MAO) inhibitor. Patients' platelet MAO activity was measured following a drug washout period before treatment. Patients with higher MAO activity had a better response to treatment, regardless of which drug was used.
(Am J Psychiatry 1987; 144:338–340)

There has recently been much activity in trying to identify biological markers of psychiatric disorders. It is hoped that when such markers are found, they will be useful in clarifying a diagnosis as well as planning its treatment. One such putative marker has been platelet monoamine oxidase (MAO) activity. There have been reports that low platelet MAO activity is associated with affective disorders (1, 2), alcoholism (2), suicidal behavior (1), and certain personality traits such as sensation-seeking behavior and impulsivity (3). One explanation for this association involves the neurotransmitter serotonin; Oreland (4) has postulated that platelet MAO activity is a reflection of serotonin activity in the CNS, with low MAO activity indicating low central serotonergic turnover.

Besides the purported connection between platelet MAO activity and depression, there is evidence that both major classes of antidepressants, tricyclics and MAO inhibitors, affect platelet MAO activity. While the effect of MAO inhibitors on MAO is clearly stated in their name, tricyclics, to a lesser degree, have also been reported to inhibit MAO-B activity (MAO-B is the form of enzyme found in platelets) (5). To our knowledge, there have been few studies examining the implications of platelet MAO activity on treatment with antidepressants. Giller et al. (6) found that responders to isocarboxazid had higher MAO activity than nonresponders. Another report (7) found that patients with certain clinical features associated with higher MAO activity responded better to MAO inhibitors than those who did not possess such features. On the other hand, Robinson et al. (8) reported that patients with higher MAO activity were less responsive to antidepressant treatment. Since antidepressants are believed to affect central monoaminergic activity, which in turn may be related to MAO activity, it seems plausible that there may be a potentially useful relationship between platelet MAO activity and response to antidepressants.

METHOD

Our study to explore such a relationship was conducted at the Depression Studies Program of New York University, a research academic facility for the study and treatment of affective disorders. Men and women, 55 years of age and older, were accepted into the study if they were consensually diagnosed by two psychiatrists as suffering from major depressive disorder (unipolar) as defined by Research Diagnostic Criteria (9). A score of 16 or greater on the Hamilton Rating Scale for Depression (21 items) was also required for inclusion. During the initial screening, the treatment plan and study requirements were fully explained, and informed consent was obtained. Patients were not included if they showed evidence of moderate to severe dementia, drug or alcohol dependence, serious neurological disorder, or another major psychiatric disorder. The mean±SD age of the patients was 63.83±6.06 years. They had had a mean±SD of 2.86±4.73 prior episodes of depression.

Patients who entered the study were administered placebo during a single-blind washout period of at least 7 days. If still depressed, they entered a 7-week period in which they were randomly assigned treatment with nortriptyline, phenelzine, or placebo under

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Supported in part by NIMH grant MH-35196 to Dr. Georgotas.

The authors thank Ms. Irene Chang for her help as project coordinator, Ms. Ethel Edelstein for secretarial assistance, Ms. Mary Armour and Ms. Joan Kuster for technical assistance on MAO assays, and Mr. David Allen, Ms. Audrey Meister, Ms. Brenda Katos, and Ms. Rhoda Lonow for technical assistance on nortriptyline assays.

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double-blind conditions. Doses were adjusted to maintain a plasma level of 50–170 ng/ml in nortriptyline patients and an MAO platelet inhibition greater than 70% in phenelzine patients for at least 2 weeks. The nortriptyline group took an average of 79.0 mg/day, while the phenelzine patients took an average of 53.9 mg/day. Most patients were treated for at least 7 weeks, and all had received at least 5 weeks of treatment. A prior analysis (10) had shown both antidepressants to be significantly superior to placebo and not significantly different from each other in the treatment of major depression for this sample population. From the antidepressant-treated group, baseline MAO platelet activity was available on 37 patients; 20 had received nortriptyline and 17 phenelzine. The outcome measure examined was the final Hamilton score; a final score of 10 or below was considered to reflect a clinical response.

Venous blood was collected for assay in an EDTA-containing polypropylene syringe (Sarstedt) and immediately centrifuged at 200 g for 10 minutes at room temperature. The platelet-rich plasma was transferred, with a plastic pipette, into a polypropylene test tube and centrifuged at 2,500 g for 10 minutes at 4°C. The platelet pellet was resuspended in 1 cc of H_2O by vortexing, and then 1 cc of 1.8% NaCl was added. It was recentrifuged at 2,500 g for 10 minutes at 4°C, and then the pellet was resuspended a second time in 2 cc of Krebs-Ringer EDTA buffer. After another centrifugation, the pellet was resuspended in 1 cc of 0.9% NaCl and frozen at −80°C until assay 3 to 4 days later.

The platelet MAO activity was measured by a modification (11) of the method of Wurtman and Axelrod (12) that employed the B-type substrate phenylethylamine-^{14}C. The reaction mixture, phenylethylamine-^{14}C at 14μM in sodium phosphate buffer (pH of 7.8), was incubated for 3 minutes at 30°C and terminated by the addition of 6 N HCl. The product was extracted into 2 cc of toluene and quantified by counting aliquot in a liquid scintillation counter. The reaction was found to be linear for up to 8 minutes and at protein concentrations of 10–1,000 μg. MAO activity was calculated as nmol product/hour per milligram of protein. Protein was measured by the method of Lowry et al. (13). The coefficient of variation with split samples was <2%. The assayist was blind to both the patients' treatment and their clinical status, and the clinicians were blind to the assay results.

RESULTS

The predictive effect of baseline MAO platelet activity on the final Hamilton score was examined with a multiple regression analysis; the baseline Hamilton score was partialed out. A difference in efficacy between the two antidepressants and an interaction between medication and MAO activity were also tested in the analysis. Baseline MAO activity was found to be significantly (negatively) correlated with the final Hamilton score (simple $r=-.24$; $F=7.41$, $df=1, 32$, $p<.05$). No significant difference in efficacy between the two antidepressants or MAO Activity × Medication interaction was found; the latter result indicated that higher MAO activity predicted a better response to both the tricyclics and MAO inhibitors. There were no significant correlations between baseline Hamilton score and either MAO activity (Pearson $r=.046$, $df=42$, $p=.39$) or final Hamilton score (Pearson $r=.14$, $df=39$, $p=.20$).

Twenty-three patients (62%) were antidepressant responders and 14 (38%) were nonresponders. Table 1 shows baseline MAO activity and Hamilton scores of the responders and nonresponders. The MAO activity at baseline was significantly lower in nonresponders than in responders (mean±SD=30.91±15.3 versus 46.93±19.0; $t=2.54$, $df=34$, $p=.016$). There was no significant difference between responders and nonresponders in sex ($\chi^2=0.08$, $df=1$, $p=.77$), age ($t=-0.90$, $df=35$, $p=.37$), or anxiety as measured by items 10 and 11 on the Hamilton scale ($t=-0.55$, $df=34$, $p=.59$); these factors have been linked to differences in platelet MAO activity (1). In addition, there was no significant difference between responders and nonresponders in baseline Hamilton score ($t=-0.99$, $df=37$, $p=.33$).

DISCUSSION

Our findings show that depressed patients with low MAO activity are less responsive to antidepressant treatment than those with higher MAO activity. This appears to be independent of whether a tricyclic or MAO inhibitor is used. Our findings are in agreement with those of Giller et al. (6); however, only an MAO inhibitor was used in that study. The meaning of these results in terms of central monoaminergic activity is yet to be explored. The fact that both classes of antidepressants are known to inhibit MAO may in some way be related to the antidepressant effect. Perhaps patients with high MAO activity provide more of a substrate on which the drug is to work and, therefore, have a greater chance of having their mood changed by the drug. Another possibility is that since at least some antidepressants are believed to mediate their effects through serotonin, a high central serotonin turnover, as reflected by higher MAO activity, may permit the antidepressants to be more effective. Personality disturbances have been found to be associated with lower MAO activity, and perhaps the recovery from a major depression is much more difficult in the face of these psychological difficulties. Since our population was an older one, and age itself is known to affect MAO activity (1), it is not certain whether these results can be generalized to younger populations, although the findings of Giller et al. (6) suggest that this may be possible. The possibility that the diagnosis of depression may be made less heterogeneous, with the selection of patients who are optimal responders to

TABLE 1. Baseline Platelet MAO Activity and Hamilton Depression Scores of Patients Who Did and Did Not Respond to Antidepressant Treatment

Group and Subject	Age (years)	Sex	Treatment	Baseline MAO Activity (nmol product/hr/mg protein)	Hamilton Score	
					Baseline	Final
Responders						
1	71	F	Phenelzine	56.8	24	3
2	69	F	Nortriptyline	64.0	31	2
3	69	F	Phenelzine	47.5	29	6
4	62	M	Phenelzine	40.6	30	0
5	61	F	Nortriptyline	54.4	21	7
6	68	M	Nortriptyline	44.1	25	1
7	67	F	Phenelzine	55.9	21	10
8	55	F	Nortriptyline	60.9	28	9
9	72	M	Phenelzine	41.4	23	5
10	62	F	Phenelzine	87.5	22	3
11	65	F	Phenelzine	46.3	17	10
12	58	F	Nortriptyline	35.5	18	5
13	55	M	Nortriptyline	29.9	25	7
14	60	M	Phenelzine	30.8	30	2
15	65	M	Phenelzine	29.0	25	7
16	55	F	Nortriptyline	88.4	21	6
17	71	F	Nortriptyline	34.7	17	9
18	57	F	Nortriptyline	56.8	19	3
19	67	M	Nortriptyline	62.2	18	0
20	56	F	Nortriptyline	6.9	18	2
21	74	F	Nortriptyline	41.6	20	9
22	65	M	Phenelzine	21.7	18	6
23	63	M	Nortriptyline	42.4	17	6
Nonresponders						
1	72	F	Nortriptyline	45.3	28	25
2	67	M	Phenelzine	39.9	22	19
3	61	F	Nortriptyline	3.5	34	24
4	50	F	Phenelzine	41.2	15	22
5	76	F	Nortriptyline	36.9	26	19
6	63	M	Nortriptyline	43.8	26	15
7	68	F	Phenelzine	45.7	19	18
8	65	F	Phenelzine	37.3	22	11
9	63	F	Phenelzine	28.3	32	11
10	66	F	Nortriptyline	17.5	24	19
11	56	F	Phenelzine	18.7	19	19
12	62	F	Nortriptyline	21.3	19	13
13	67	M	Nortriptyline	4.4	31	25
14	59	F	Phenelzine	48.9	20	20

antidepressants, makes these findings interesting. However, they should be interpreted cautiously until futher replication.

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A Biopsychosocial Approach to Treating Patients With Affective Disorders

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The authors describe the development of an affective disorders consultation service that implemented a biopsychosocial model of subspecialty consultation within a university-affiliated community mental health center. They retrospectively analyzed the first 2 years of consultations, assessing the process of consultation and examining patterns of consultee inquiries and consultation recommendations. Consultants recommended combined psychopharmacologic and psychodynamic therapies for most patients and found psychodynamic psychotherapy strikingly overlooked by consultees, all of whom were psychiatrists or other mental health professionals. This evaluation documents the psychiatric consultees' deemphasis of the biopsychosocial perspective in clinical practice.
(Am J Psychiatry 1987; 144:341–344)

The biopsychosocial model of clinical care described by Engel (1) postulates that a biochemical or biophysical defect, while a necessary condition of disease, is not by itself sufficient to explain the human experience of illness. In this model, psychological, social, cultural, and biological factors are all viewed as crucial. We developed a subspecialty consultation service committed to integrating different conceptual approaches to clinical problems (i.e., psychodynamic, biological, psychosocial) in sharp contrast to a subspecialty service devoted to one conceptual diagnostic and treatment approach (a phobia clinic, for example, which endorses biological approaches exclusively and does not equally emphasize a psychodynamic perspective).

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Supported by NIMH grant MH-15413 and by a grant from the George Harrington Trust Research Development Fund.
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Sources of difficulty in achieving such integrated psychological and physical care have been described by Brown and Zinberg (2), who suggested that the biomedical perspective may deemphasize psychosocial factors in approaching illness. Docherty et al. (3) elucidated the difficulties inherent in maintaining an integration between psychotherapy and pharmacotherapy. They stated that the key issue "involves a distinction between relating to the patient as a diseased organ or object of study (subject-object mode) or as a disturbed person (subject-subject mode)," contending that psychobiological integration is possible but requires a balanced "bimodal relatedness."

This study, based within a metal health facility, objectively documents the degree to which the biopsychosocial model of patient care was used in clinical practice by our consultees, all of whom were psychiatrists or mental health professionals.

METHOD

The Massachusetts Mental Health Center, a community mental health center that serves an ethnically diverse population of 200,000 in the inner city and near suburban communities of Boston, is a collaborative enterprise between the Commonwealth of Massachusetts and the Harvard Medical School. The center has an active walk-in and outpatient clinic complemented by day hospital and intensive care programs. A multidisciplinary treatment team serves inpatients and outpatients.

The Affective Disorders Consultation Service (ADCS) was established in July 1978 to accomplish two primary goals: 1) to provide patients with direct subspecialty consultation and assessment by staff psychiatrists on the ADCS team and 2) to enhance the expertise of psychiatric residents and clinical mental health professionals in the diagnosis and treatment of affective disorders.

The ADCS team consisted of four senior psychiatrist staff consultants with a wide range of expertise in neuropsychopharmacology, psychodynamic psychotherapy, epidemiology, and psychosocial aspects of evaluation and treatment of affective illness. A junior

staff psychiatrist, the primary ADCS consultant, interviewed patients referred for consultation. This physician was responsible for the daily functioning of the service but shared clinical responsibility for case consultation with two other junior staff consultants. A clinical psychologist and a research social psychologist, respectively, provided consultation regarding psychological assessment and collection of clinical research data.

The defining characteristic of our service was a weekly 90-minute case presentation conference conducted by the senior consultants and attended by consultees and other ADCS staff. The objective of the weekly meeting was to arrive by consensus at a clinical formulation, including a *DSM-III* diagnosis, and to recommend a specific treatment plan. The junior staff psychiatrist presented the case and dictated a comprehensive note that included diagnostic impression, case formulation, and recommendations. As the service developed momentum, members of the hospital staff joined consultees in the rounds. The educational value of a supervisor and supervisee retrospectively examining their psychotherapy case supervision before a group of trainees has been described (4). Our consultation format represented an elaboration of that idea—modelling a group collaboration around a consultation. We sought to emphasize differing perspectives, highlight key clinical decisions, and invite conflicting viewpoints.

At the completion of the first year of the ADCS, we reviewed and examined our performance. We conducted a retrospective chart review that recorded referral source, the presenting questions, sociodemographic characteristics, presenting clinical symptoms (as measured by the Hamilton Rating Scale for Depression administered to dysphoric patients at the time of consultation), major medical illness, *DSM-III* diagnoses (axis I and II), and the ADCS consultants' recommendations for treatment.

To ensure that we had reliably extracted this information from the records, we selected 40 cases for interrater reliability. Four coders (three psychiatrists and a psychologist) completed a codebook for each of the 40 cases, and ratings were then compared for all possible pairs of raters on each codebook item. Using a criterion of at least 90% of rated cases showing perfect agreement in at least three of four possible ratings pairs, we identified variables suitable for further study. For items that were found less reliable, a single rater reviewed all cases and extracted the appropriate information.

We analyzed 189 consultations done from July 1978 to July 1980. Of these, 33% came from our inpatient population, and 67% were referred from outpatient treatment. Of the 189 patients, 49% were referred by psychiatric residents, 3% by staff psychiatrists, 18% by psychiatric social workers, 10% by psychologists or psychiatric nurses, and 20% by other sources including affiliated community clinics and private referrals.

The ADCS sample consisted of 67 male and 122 female patients ranging in age from 13 to 82 years. Their mean±SD age was 38.5±15.0 years. The sample was evenly distributed across social classes (Hollingshead [5] classes I and II, 26%; class III, 18%; class IV, 32%; and class V, 24%). The majority (85%) of the patients were Caucasian.

TABLE 1. *DSM-III* Diagnoses in 184 Patients

Diagnosis	*N*	%
Major depression		
Pure	28	15.2
With personality disorder	22	12.0
With dysthymic disorder	14	7.6
With personality and dysthymic disorder	15	8.2
Schizophrenia	17	9.2
Schizoaffective disorder	17	9.2
Bipolar disorder	34	18.5
Personality disorder	24	13.0
Dysthymic disorder	5	2.7
Personality and dysthymic disorder	3	1.6
Other	5	2.7

RESULTS

Of the 189 patients, 184 were classified by using *DSM-III* criteria: 43% were classified as having major depression; 18.5%, bipolar disorder; 9%, schizophrenia; 9%, schizoaffective disorder; and the remaining 20% predominantly as having *DSM-III* axis II personality disorders without major affective disorder. Of the patients diagnosed as having major depression, a majority had a superimposed personality and/or dysthymic disorder (table 1).

To assess the process of consultation, we analyzed trends in consultee inquiries and our recommendations to determine the degree to which they seemed congruent with the biopsychosocial problems of our patients. The consultee sought the consultant's diagnostic impression of the patient in 61.5% of cases. Inquiries regarding medication management were made in 85% of cases. Inquiry as to the appropriateness of evaluative measures (e.g., advisability of psychological testing) occurred in 13% of cases; questions regarding patient management strategies (full- versus part-time hospitalization, restrictions, readiness for discharge) were present in 14% of cases; requests for consultation related to psychotherapy were present in fewer than 2% of cases. The vast majority of questions raised by psychiatrists and mental health professionals referring cases were related to diagnostic assessments and medication management; strikingly, there was minimal inquiry regarding psychotherapy.

In contrast, the ADCS consultants showed much more concern with psychotherapeutic interventions. Consultants recommended the initiation of individual psychotherapy in 69% of all cases and modification of the ongoing psychotherapeutic approach in an additional 13%.

Recommendations regarding psychopharmacology

TABLE 2. Consultant Recommendations and Consultee Inquiries in Three Clinical Spheres for 189 Patients

Clinical Sphere	Consultant Recommendations	Consultee Inquiries	Recommendations/ Inquiries Ratio
Psychotherapy	153	3	51.0
Psychopharmacology	175	160	1.1
ECT	25	5	5.0

were made in 93% of cases, and recommendations to consider ECT occurred in 13% of cases. Initiation of tricyclic antidepressants, antipsychotic medications, and lithium carbonate was recommended in 47%, 33%, and 25% of cases, respectively.

Further medical evaluation was deemed necessary by consultants in 44% of cases, and psychological testing (projective or neuropsychological) was recommended for 25% of patients. Laboratory tests such as lithium or antidepressant blood levels, platelet monoamine oxidase activity, or urinary levels of 3-methoxy-4-hydroxyphenylglycol (MHPG) were suggested in 13% of cases.

We were impressed that the ADCS consultants drew attention to clinical issues that appeared to be overlooked by consultees, particularly those related to psychodynamic psychotherapy. To underline this finding, we calculated a recommendation/inquiry ratio in three clinical spheres—questions related to psychotherapy, psychopharmacology, and ECT. The numerator was the consultant recommendations and the denominator was the consultee inquiries. Thus, the larger the ratio, the more interest shown by consultants than by consultees in that particular intervention. As shown in table 2, the largest ratio by far was obtained for psychotherapy-related recommendations, underlining the marked discrepancy between the consultants' and the consultees' concern over issues of psychotherapy.

DISCUSSION

The key finding pertaining to diagnostic data was that major depression superimposed on personality disorder and/or dysthymic disorder was more commonly seen than pure major depression. This again underlined the importance of integrating biomedical and psychodynamic perspectives in formulating treatment planning.

Overall, the sample showed an even distribution across occupational and social class levels. The ratio of female to male patients was approximately two to one. The age and gender characteristics of the ADCS sample are in keeping with previous reports of the epidemiology of the depressive disorders (6).

We were impressed by a striking pattern of undertreatment of depression both by psychodynamic and somatic therapies. Psychiatrists and mental health professionals seeking consultation deemphasized psychodynamic psychotherapy and ECT as well as more extensive medical assessments in approaching patient care. The tendency toward undertreatment of patients with affective illness has been previously reported in the context of a community survey (7), and treatment outcome data have underlined the value of combining interpersonal psychotherapy and psychopharmacological approaches (8).

Our study documented that consultees to our service, psychiatrists and mental health professionals, had deemphasized psychodynamic psychotherapy in the treatment of affective illness and had not implemented a biopsychosocial approach to patient care. This suggests that psychiatric services should attempt to objectively assess the actual implementation of these principles of patient care.

Perhaps the complexity of patients encountered and the relative inexperience of many consultees contributed to therapeutic uncertainty and indecision, but, as Karasu (9) has emphasized, broader conceptual issues need to be addressed to understand the difficulties inherent in providing truly integrated care to psychiatric patients, incuding conceptual antagonisms rooted in the mind-body dichotomy. In a discussion of the reaction and proaction models of clinical care, Gill (10) has clarified the mental and emotional agility required to be a flexible clinician. The reaction model emphasizes the patient as a passive recipient of a treatment technique, be it pharmacological or behavioral; the proaction model, by contrast, focuses on the patient as a collaborator in the therapeutic process, responsible for attempting to understand the conscious or unconscious factors that may be motivating dysfunctional behavior. Clinical practice demands that the clinician have the ability to shift from one model to the other and to integrate both as required by the patients' needs.

Subspecialty consultation services can become an educational forum in which psychiatric clinicians are sensitized to these issues. The evaluation of our subspecialty consultation service provided baseline data that underlined a role for further educational efforts to enhance the psychiatric consultees' understanding of the synergistic effects of psychodynamic psychotherapy and biological treatments.

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Long-Term Effects of Extreme Situational Stress on Sleep and Dreaming

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Sleep data were obtained on 11 patients who had survived traumatic events and who complained of sleep disturbances. Each was awakened from REM and non-REM sleep for dream recall. The patients had lower sleep efficiency indices (because of prolonged sleep latency and larger amounts of "awake" plus "movement" time within sleep periods), shorter REM time, and longer REM latencies than did control subjects. Four of the 11 patients had REM- and non-REM-related nightmares, which, in two sea disaster patients, were associated with REM-related motor activity. The rest of the patients had unusually low dream recall in spite of high eye movement density.

(Am J Psychiatry 1987; 144:344–347)

While the concept of stress and the various outcomes of stressful life events are still subjects of controversy and debate (1, 2), there is unanimity in the opinion that extremely stressful environmental conditions may lead to short- and long-term disruption of many systems in the individual (3–10).

Few studies have objectively investigated the effects of extreme situational stress on sleep. Greenberg et al. (11) studied the sleep structure of patients with war neuroses and found a significant correlation between REM latency and defensive strain, which was the score of the degree of recruitment of defenses in handling stress. They also found that these patients had poor dream recall after REM awakenings and a lack of nightmares in the laboratory in spite of high REM densities. In contrast, we reported (12) a significant lengthening of REM latency and a significant reduction of REM time in 11 postcombat patients investigated in the sleep laboratory 2–2½ years after their traumatic experiences. Two of these patients suffered from REM-interruption insomnia, and in some we found increased body movement and intrusion of EEG arousal patterns into sleep (13).

More recently, van der Kolk et al. (14) compared the occurrence of nightmares in Vietnam veterans with posttraumatic stress syndrome and in veterans without combat experience who suffered from lifelong nightmares. Only two of their 35 patients in the posttraumatic stress group had recordings made in a sleep laboratory. Both had REM- and stage-2-related nightmares associated with automatic motor behavior. Stage-2-related nightmares were also reported in three combat fatigue patients by Schlosberg and Benjamin (15). Similar results were reported in preliminary form by Kramer et al. (16).

There have been about 20 nonlaboratory studies on the effects of different types of civilian disasters on sleep and dreaming. Generally, these indicated that at least some trauma-related sleep disturbances are universal. Nightmares and fearful dreams, for instance, were reported in patients suffering from combat neurosis (4, 5, 8), survivors of natural disasters (10), and survivors of Nazi concentration camps (6). The fact that different studies were conducted at different times after the traumatic experiences makes it difficult, however, to determine whether sleep disturbances were modified with the passage of time. Also, it is not known how many of the nightmares and frightening

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dreams were the expression of attempts to "master the trauma" and how many were, in fact, the outcome of a gradual deterioration.

In this paper we describe the results of a sleep laboratory study of three different types of survivors: Holocaust survivors, sea disaster survivors, and postcombat patients. Sleep structure and REM-elicited dream recall were investigated to determine whether patients exposed to different types of extremely stressful situations had common characteristics.

METHOD

Eleven patients participated in the study. Five of them (ages 45 to 68 years) were survivors of Nazi concentration camps; of these, three had a clinical picture of depression and were being treated with tricyclic antidepressants. For medical and ethical reasons, treatment was continued during the study. The two other patients from this group complained of sleep disturbances and recurrent nightmares in the past, but all medications that could possibly affect sleep were discontinued at least 10 days before the study.

Four patients, ages 33, 35 (two patients), and 44, suffered from combat neurosis. One of them had shown symptoms since 1973, following the Yom Kippur War. In the others, the traumatic history dated from 1981, after a combat experience involving terrorist activity. All showed typical posttraumatic stress disorder with a depressive tendency. All drug treatment (doxepin, 75 mg, for one and a minor tranquilizer for the others) was stopped 2 weeks before the study began.

A third group was composed of two survivors of two separate sea disasters that had occurred 6 and 12 months before the study. These patients were 20 and 25 years old and had suffered from posttraumatic stress disorder with recurrent nightmares. One patient received 25 mg/day of chlorpromazine, and the other was treated with 10 mg/day of chlordiazepoxide. These medications continued during the study.

All patients had a detailed psychiatric and physical examination, and their written informed consent was obtained before the study. The postcombat and sea disaster patients were studied during their hospitalization; the Holocaust survivors were studied as outpatients.

Each of the patients slept in the laboratory for 2–5 nights. Polyhypnographic recordings included EEG, electro-oculogram, electromyogram, and ECG. In addition, respiration was monitored by a nostril thermistor and a respiratory belt, and leg movements were monitored by an accelerometer. Whenever a patient was available for 4 or 5 nights, this procedure was followed: an initial adaptation night, a baseline night, and then 2 or 3 nights of dream report collection. For two patients, whose data were recorded for 2 nights, the first night was the adaptation night.

For dream reports, the patients were awakened 10–15 minutes after the beginning of every REM period except the first and were requested to report everything that was going on in their minds just before awakening. Accounts of dreams were also collected after each spontaneous awakening. Sleep records were scored according to standard criteria in 30-second epochs (17). Eye movement density in REM sleep was measured as reported previously (18). Briefly, REM periods were divided into 1-minute epochs, which were then subdivided into 20 3-second intervals. For each minute of REM sleep, the percentage of 3-second intervals containing at least one horizontal eye movement was the density score. Control data for the postcombat and sea disaster patients were obtained from nine age-matched normal men who participated in a different study. Control data for the concentration camp survivors were taken from the work of Williams et al. (19).

RESULTS

Tables 1 and 2 present the mean sleep data for the Holocaust survivors and the postcombat and sea disaster survivors (grouped together) and the control data. The reason for combining the last two patient groups was the similarity of their sleep data and their ages. In comparison with age-matched controls, all patients had low sleep efficiency indices, caused by a prolongation of sleep latency and larger amounts of "awake" plus "movement" time within sleep periods. This was particularly evident in the sea disaster and postcombat patients. REM sleep was significantly shorter in all patients than in controls, but comparably longer REM latency was seen only in the postcombat and sea disaster patients. The patients did not spend more time in sleep stages 1 and 2 than the controls did (table 1).

In four of the 11 patients, there were laboratory-documented REM- and non-REM-related nightmares. In the two sea disaster survivors, there was clear evidence of REM-interruption insomnia. In one, REM periods were fragmented by multiple arousals associated with violent body movements and vocalizations, which on two occasions were accompanied by falling from bed. Whenever this patient was awakened from these "stormy" REM periods, he reported having vivid nightmares in which he "relived" the sea disaster. The second sea disaster survivor similarly reported vivid nightmares related to the disaster whenever he awakened from REM sleep. The third patient was a 45-year-old concentration camp survivor who had gone through the atrocities of the Holocaust in his childhood. He awoke several times spontaneously from both REM and non-REM sleep, and each time he reported the same anxiety dream, in which he was being haunted by his persecutors. This was a repetition of an actual traumatic experience he had had at age 6, more than 39 years earlier. He also reported the same haunting dream when awakened from REM periods.

TABLE 1. Sleep Data of Patients Who Were Holocaust Survivors (N=5) and of a Control Group (N=12)

Measure	Patients		Control Group[a]		Analysis t (df=15)	p
	Mean	SD	Mean	SD		
Total sleep time (min)	296.7	32.4	389.8	49.5	3.64	<.01
Sleep latency (min)	16.1	16.2	11.9	10.5	0.59	n.s.
REM latency (min)	102.3	28.3	84.8	19.4	1.38	n.s.
Sleep efficiency (%)	75.5	9.5	92.0	4.0	4.73	<.01
"Awake" plus "movement" time (%)	15.9	7.9	4.3	2.3	4.36	<.01
Stage 1 sleep (%)	5.2	2.3	7.6	3.9	1.21	n.s.
Stage 2 sleep (%)	55.2	7.8	61.7	10.3	1.19	n.s.
Stages 3 and 4 sleep (%)	14.7	3.4	4.9	7.7	2.57	<.05
REM sleep (%)	14.9	4.0	21.5	4.0	2.9	<.02

[a]Control data are from Williams et al. (19) for the 50–59-year age group (men).

TABLE 2. Sleep Data of Post-Combat and Sea Disaster Patients (N=6) and of a Control Group (N=9)

Measure	Patients		Control Group[a]		Analysis t (df=13)	p
	Mean	SD	Mean	SD		
Total sleep time (min)	253.8	16.3	377.4	23.6	10.4	<.01
Sleep latency (min)	41.3	2.7	19.6	16.2	3.03	<.02
REM latency (min)	136.3	33.9	68.6	15.2	4.89	<.01
Sleep efficiency (%)	71.1	2.9	91.1	3.2	11.5	<.01
"Awake" plus "movement" time (%)	16.5	6.0	4.5	2.8	4.85	<.01
Stage 1 sleep (%)	4.2	2.9	2.1	1.7	1.64	n.s.
Stage 2 sleep (%)	47.4	7.3	42.2	8.1	1.18	n.s.
Stages 3 and 4 sleep (%)	21.3	9.9	28.4	4.9	1.71	n.s.
REM sleep (%)	10.3	2.9	22.6	4.5	5.52	<.01

[a]Control data are from Lavie et al. (12).

The fourth patient who experienced nightmares in the laboratory was a 33-year-old combat-reaction patient. This patient reported combat-related nightmares both when awakened from REM sleep and upon spontaneous awakening from sleep stage 2. For instance, he awoke from REM sleep and reported the following dream: "I was taken as a POW and executed. Somehow, I also saw a burnt face haunting me. This was followed by additional bombing, smoke, shells, and helicopters." This patient had been subjected to bombing by helicopters during the war, and many of his comrades had been killed during the raid.

In contrast to these four patients, none of the others had any nightmares or night terrors during their laboratory nights. Surprisingly, their rate of dream recall was remarkably low; out of 21 REM awakenings there were only four dream reports with some content. In the rest of the awakenings, patients denied dreaming at all. In spite of the low dream recall, the overall REM density was significantly higher ($p<.05$) than that of the control groups for the first three REM periods. The average densities were 35.4% versus 21.6% for REM 1, 37.8% versus 24.4% for REM 2, and 40.1% versus 24.9% for REM 3.

DISCUSSION

Our findings in these posttraumatic patients agreed with the sleep characteristics of postcombat patients reported by us (12, 13) and by others (11, 15, 16). Like Greenberg et al. (11), in seven of our 11 patients we found a very low rate of dream recall after REM awakenings despite intensive eye movement activity. Low occurrence of nightmares in the laboratory has also been described in patients who subjectively complained of nightmares (20).

Four patients had laboratory-documented nightmares. The two most significant observations concerning these patients were the REM-related motor activity and vocalization in the sea disaster patients and the occurrence of nightmares in both non-REM and REM periods in a Holocaust survivor and in a postcombat neurotic patient. Thus, in agreement with the observations of van der Kolk et al. (14), in spite of REM-related muscle atonia, one of the sea survivors showed complex motor activity during REM, which at one time resulted in an actual escape from the bedroom. Although none of the other patients showed similar REM-related motor activity, explosive motor activity could be elicited in the postcombat neurotic patient who had both REM and non-REM nightmares by abruptly waking him from sleep. This elicited behavior was seen several times when he was hospitalized. Unfortunately, we do not know whether these episodes were REM related.

Interestingly, the two patients who had both REM and non-REM nightmares suffered from persistent repeated haunting dreams. These were a realistic reliving of traumatic events, including many elements from the actual trauma. Since we are not aware of any other sleep laboratory study of repeated haunting dreams, we cannot state with certainty whether the invasion of nightmares into non-REM sleep is specific to this kind of dreams.

In contrast to the four patients who suffered from laboratory-documented nightmares, the rest of the patients had a surprisingly low recall rate. The few dreams that were recalled were brief and dealt with trivial daily events. The lack of dream recall was particularly surprising in view of the high REM densities. Dissociation between REM activity and dream recall has been reported by Antrobus et al. (21). It is possible that there is an inverse relationship between recall and density, both when low recall represents a "state" variable, as in our study and that of Greenberg et al. (11), and when it represents a "trait" variable, as in the study of Antrobus et al.

Do the present observations advance our understanding of the short- and long-term effects of extremely stressful events on sleep and dreams? Although they do not provide definite answers, they nevertheless indicate that the amount of time since the trauma is an important factor with regard to the type of sleep and dream disturbances. The two sea disaster survivors and the postcombat neurotic patient who suffered

from REM-interruption insomnia were investigated less than 18 months after their traumas. The patient who displayed the most impressive REM-related motor activity was studied just 6 months after the sinking of the ship. Thus, it can be suggested that the intensity of the REM-related nightmares, the involvement of motor components, and the fragmentation of REM sleep by multiple awakenings are characteristics of the immediate responses to the trauma.

The long-term modification of sleep, however, can be developed in at least two different ways: either a complete or a nearly complete suppression of dream recall, concomitant with shorter REM time and longer REM latency, or persistent REM and non-REM-related nightmares incorporating elements from the actual trauma. Both types of responses were seen in our previous study (12) of the sleep structure of post-combat neurotic patients conducted a few years after the trauma. In all but two patients in that study there was significantly less REM time than in an age-matched control group, and there was no recurrence of nightmares in the laboratory. Two patients suffered from REM-interruption insomnia. However, no definite relation could be detected between the length of time since the trauma and sleep measures.

We have no information yet about the adaptive value of either one of the long-term modifications. Except for two patients, all the patients in the present study showed a lack of adaptation and coping. One of the two adapting patients was the Holocaust survivor, who suffered from the repeated haunting dream. The other was a patient with no dream recall at all. Much more information is needed before a firm conclusion can be reached on the adaptive value of the post-traumatic long-term modifications in sleep and dreaming.

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Seriously Depressed Preschoolers

Javad H. Kashani, M.D., and Gabrielle A. Carlson, M.D.

In a prospective and comprehensive evaluation (including DSM-III *diagnoses) of 1,000 preschoolers in a child development unit, nine children were found to meet the criteria for major depressive disorder. The symptoms of these children are described and compared with those of a control group of children from the same sample. The diagnosis of major depressive disorder was associated with physical symptoms, including somatic complaints, and the likelihood of parental abuse or neglect.*

(Am J Psychiatry 1987; 144:348–350)

Despite impressive advances during the past decade in the study of childhood depression from biological, genetic, and epidemiological perspectives (1–8), preschool-age children have received scant attention. Relative disregard for this age group is understandable, since preschoolers have only a limited ability to conceptualize and can say little regarding the onset and duration of their symptoms and feelings (9). Furthermore, some are unable to distinguish between sadness and happiness or have difficulty verbalizing their feelings.

Such limitations, as well as a lack of reliable and valid assessment tools, have to date severely compromised the evaluation of depression in preschoolers. In addition, the existence of such a clinical entity has been questioned until only recently. As a result a definite clinical description and a spectrum of symptoms based on empirical studies have been lacking. In a previous report, we discussed the existence of depression and depressive-like states in a clinically referred group of preschool-age children (10, 11) and in a general population (12) and recommended that future studies address in detail the characteristics of depressed preschool-age children. The present study begins to address the phenomenology of severely depressed young children.

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METHOD

The sample consisted of 1,000 children consecutively referred to a child development unit over a 5-year period beginning in 1981. Data from the first 1,000 cases were collected to maximize the likelihood of finding an adequate sample of preschool-age children with major depressive disorder. Of these children, 19 were undergoing re-evaluation; their ages were between 7 and 9 years (although they were mentally below age 6). The remainder were between ages 1 and 6 (mean=4.2). The children were referred for a variety of reasons, including developmental delays, speech and language difficulties, and emotional and behavioral disorders. The male-female ratio approximated 2:1, and the majority were middle class (Hollingshead and Redlich's Class III) (13).

The evaluation procedure, described elsewhere (10, 14), has three components and takes 2 days to complete. The parents (or guardians) and child were interviewed jointly and individually by a child psychiatrist (J.H.K.) for at least 2 hours. More detailed psychosocial information was obtained by a social worker. Second, comprehensive testing was completed by a child psychologist, educational psychologist, speech-language pathologist, occupational therapist, and child development specialist. Finally, the child and parents were observed in a structured setting, and the details of the parent-child interaction were recorded by an observer in a setting with a one-way mirror. The final diagnosis of major depressive disorder, made only after scrutinizing this comprehensive collection of data, required complete and independent agreement between two child clinicians, one of whom was the child psychiatrist. For this study, each of the nine preschoolers so diagnosed was matched by age, sex, race, socioeconomic status, and year of evaluation with two controls selected from the original pool of 1,000 children.

RESULTS

The diagnosis of major depressive disorder was made in only nine of the systematically evaluated preschoolers (table 1 depicts other psychiatric diagnoses). Their ages ranged from 2 years 11 months to 6 years. Six were boys, and three were girls. Although structured interviews for family history of psychiatric

TABLE 1. *DSM-III* Diagnoses Other Than Major Depression of 1,000 Clinically Referred Preschoolers

Diagnosis	N	%
Condition not attributable to a mental illness (i.e., parent-child problem, other life circumstances, etc.)	273	27.3
Adjustment disorder	160	16.0
Specific developmental disorder	145	14.5
Mental retardation	73	7.3
Attention deficit disorder	65	6.5
Conduct or oppositional disorder	62	6.2
Pervasive developmental disorder	39	3.9
Anxiety disorder	22	2.2
Autism	20	2.0
Schizophrenia	4	0.4
Tourette's syndrome	3	0.3
No diagnosis	134	13.4

TABLE 2. Depressive Symptoms of Depressed and Nondepressed Preschoolers

	Depressed (N=9)		Nondepressed (N=18)		
Symptom	N	%	N	%	p[a]
DSM-III symptoms of major depression					
Appears sad	8	89	0	0	<.0001
Reported sadness	9	100	0	0	<.0001
Appetite or weight changes	9	100	0	0	<.0001
Sleep disturbance	9	100	4	22	<.0002
Fatigue	8	89	0	0	<.0001
Psychomotor agitation or hyperactivity	3	33	12	67	n.s.
Hypoactivity	7	78	2	11	<.001
Pervasive loss of interest	2	22	0	0	n.s.
Feels inadequate	4	44	0	0	<.007
Self-blame	5	55	0	0	<.0016
Expressed worthlessness	6	67	0	0	<.0003
Distractible	4	44	10	55	n.s.
Suicidal	6	67	0	0	<.0003
Other symptoms					
Cries a lot	8	89	4	22	<.0027
Irritable	7	78	6	33	<.046
Sulks	6	67	2	11	<.006
Temper tantrum	5	55	8	44	n.s.
Social withdrawal	8	89	8	44	<.04
Poor self-concept	8	89	8	44	<.04
Somatic complaints	9	100	0	0	<.0001
Fighting	1	11	12	67	<.01
Refusing to go to nursery	6	67	0	0	<.0003

[a]Significance was determined by Fisher's exact test. Twenty-two comparisons were made. To avoid an excessive experiment-wise error rate, the conservative Bonferroni approach can be made, adopting a significance level of $\alpha = .05/22 = .0023$ to signify a level of rejection.

disorders were not done, six mothers were diagnosed as being depressed, one was a drug addict (her own mother was hospitalized for depression), and the other two sets of parents could not be located.

Table 2 summarizes the frequency of depressive symptoms and relevant psychopathology in the depressed children and control subjects. The first 13 symptoms represent *DSM-III* criteria. The remaining symptoms were selected as possibly being related to depression in young children. At least in a psychiatrically referred sample of preschoolers, neither psychomotor agitation nor distractibility distinguished the depressed group. Pervasive loss of interest occurred infrequently in the sample. Using conservative estimates of significance ($p<.0023$ with Bonferroni correction), sadness, appetite loss, sleep changes, fatigue, and other symptoms, including somatic complaints, distinguished depressed preschoolers from psychiatric control subjects. The other finding was that all of the depressed children (versus 33% of the control subjects) lived in a broken home at the time of evaluation and all the depressed children (versus 22% of the control subjects) had been abused or severely neglected.

DISCUSSION

To our knowledge, this paper provides data on the largest number of clinically referred preschoolers with *DSM-III* diagnoses, especially major depression, ever reported in the literature. In addition, we would like to emphasize that the depressed children from a pool of 1,000 preschoolers were diagnosed as depressed not only on the basis of *DSM-III* criteria for children under age 6 years but also on *DSM-III* criteria for major depressive disorder in adults. The former requires either a persistent sad face or a facial expression of a dysphoric mood plus any three of the following four symptoms: problems with sleep, appetite change, hypoactivity, or apathy. The *DSM-III* criteria for major depressive disorder in adults are even stricter. At this preliminary stage of investigation of affective disorder in preschoolers, we feel more comfortable reporting on only the most seriously depressed young children. However, we acknowledge that this stricter approach may have led to underreporting.

Our data suggest that the frequency of major depression increases with age and is very uncommon in preschool children, even in a clinical population. The prevalence rate of 0.9% compares with rates of 13% (15) and 15% (16) in hospitalized preadolescents and 18.7% (17) and 28% (18) in hospitalized adolescents. Although the latter two groups represent inpatients and our subjects are outpatients, inpatient facilities for emotionally disturbed preschool children are rare and the child development unit population with its partial hospitalization component attracts as severely disturbed a population of preschoolers as one is likely to find. Epidemiological studies of general populations of children also confirm this finding. Only one in 350 preschoolers (from two different studies) met the criteria for major depression (12, 19). This increased to 1.8% in 9-year-olds (20) and 4.7% in the 14- to 16-year-olds (21).

The change in phenomenology through childhood is also interesting. Somatic complaints as a manifestation of depression, which occurred in all of our preschoolers, diminish with age. Ryan (1985 unpublished work)

found somatic complaints significantly more frequently in preadolescents (85%) than in adolescents (67%) ($p<.04$), and Carlson and Strober (22) noted that between adolescents and adults, somatic complaints decreased from 50% to 25% ($p<.02$). This may imply that the younger the child, the more likely he or she is to express the pain of depression with physical symptoms. It certainly suggests that family physicians and pediatricians seeing children with medically ambiguous abdominal, head, or chest pain should consider depression in the differential diagnosis (23, 24). We conclude, as did Rutter (25), that physically unjustified or exaggerated complaints develop against a background of misery, unhappiness, or overt depression. We therefore recommend that frequent somatic complaints be considered one of the symptom clusters of depression in preschoolers.

The frequency of physical abuse and neglect in populations of children with major depression has not been systematically studied. Whether our 100% frequency finding in preschool-age children is unique to this age group remains to be seen. This study presents data suggesting a strong relationship between physical abuse and neglect and symptomatology of major depressive disorder in preschool-age children. Kazdin et al. (26) reported somewhat similar findings in that physically abused children evidenced significantly lower self-esteem, greater depression, and more negative expectations of their future than a control group of children who were not abused. Reports of suicidal behavior in preschool-age children also document frequent physical abuse (27). We hypothesize that the helplessness, fear, and frustration experienced by abused preschoolers by virtue of their small size, limited abilities, and immature defenses may increase their vulnerability to depression. This vulnerability may be increased further by high levels of familial psychopathology (as witnessed in our sample), which itself is depressive in nature. Certainly the impact of parental mental illness (through abuse, neglect, inconsistent parenting, and other psychosocial stressors) on the development of depression has been noted before (28) and in this age group should be of serious concern.

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A Field Trial of *DSM-III-R* Psychoactive Substance Dependence Disorders

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The authors field-tested proposed criteria for diagnoses of psychoactive substance use disorders in the revision of DSM-III (DSM-III-R) *and compared them with* DSM-III *criteria in a treated group of 83 patients. They found a high level of agreement between the diagnostic systems in rates of diagnosis and in the individuals receiving the diagnosis. The greatest cross-system agreement occurred when the minimum number of symptoms required to make the* DSM-III-R *diagnosis was set at three. Discrepant diagnoses between systems related to 1) removal of social consequences as a requirement for the* DSM-III-R *diagnoses, 2) less emphasis on physiological tolerance in* DSM-III-R, *and 3) disagreement in subjects with mild symptoms.*
(Am J Psychiatry 1987; 144:351–355)

Changes in *DSM-III* are being made by APA in preparation for a revised edition, *DSM-III-R*. Although many sections have been revised in only minor ways, the section on substance use disorders has been changed substantially (1). Briefly, *DSM-III* divided substance use disorders into two types: 1) abuse, requiring a pattern of pathological use and social or occupational impairment, and 2) dependence, requiring either physiological tolerance or withdrawal and, in addition, pathological use and/or social or occupational impairment for some substances.

In *DSM-III-R*, several changes have been made. First, the distinction between abuse and dependence has been removed and a single category of dependence has been defined. Second, the format of the criteria has been changed to a diagnostic index so that no single symptom is required for a diagnosis of psychoactive substance dependence. Third, the same set of criteria applies to all substances. Fourth, the criteria for dependence have been broadened to include cognitive and behavioral symptoms (2, 3). Finally, a system has been provided for denoting severity of dependence as "in remission," "mild," "moderate," or "severe." As shown in appendix 1, nine criteria for substance dependence have been defined; three or more of these criteria are required to make the diagnosis.

Although large-scale field trials were not part of the *DSM-III-R* revision process, we felt that field-testing was essential for the section on psychoactive substance use disorders because of the major revisions that have been made. The field trial was to serve three purposes:

1. To evaluate the effect of the new criteria on the rates of substance use disorders diagnosed. Several members of the advisory committee working on the section on psychoactive substance use disorders expressed the concern that the new criteria would not be adequately inclusive of individuals who had qualified for a *DSM-III* diagnosis of abuse, leaving them without the possibility of receiving a substance use diagnosis despite having substantial consequences of their substance use. A second concern was that a change in criteria which greatly changed the rates of the diagnoses and of individuals who might receive the diagnoses would undermine the value of major surveys of mental disorders using *DSM-III* criteria (e.g., the National Institute of Mental Health [NIMH] Epidemiologic Catchment Area Program [4]).
2. To assess the reasons for any diagnostic discrepancies between the *DSM-III* and *DSM-III-R* systems to determine if critiques of *DSM-III* are adequately addressed by the new criteria. Some key critiques of *DSM-III* criteria included too great an emphasis on tolerance as a criterion and the difficulties inherent in basing diagnoses on social consequences of a disorder (1).
3. To determine the optimum number of criteria to use as a cutoff point for a *DSM-III-R* diagnosis. The decision to use three or more criteria was based on the judgment of the advisory committee and not on empirical evidence. In the field trial reported here we attempted to evaluate the impact on rates and agreement with *DSM-III* of raising or lowering the number of criteria required in *DSM-III-R*.

Two settings were chosen for a field test. The first

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Supported in part by Research Scientist Development Award DA-00089 to Dr. Rounsaville from the National Institute on Drug Abuse.

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was an inpatient psychiatric unit in which substance abuse was seldom the primary focus of treatment, chosen to test the system's ability to discriminate between patients with and without a substance use disorder. The second was an outpatient substance abuse treatment unit to which substance abusers of all types applied for treatment, chosen for the high density of individuals likely to receive a substance use diagnosis.

METHOD

Subjects were interviewed at the two settings. Forty-one patients were interviewed on the inpatient unit of a community mental health center that treats patients with a range of diagnoses for up to 28 days. Forty-two patients applying for treatment were interviewed at an ambulatory substance abuse treatment unit. In both settings patients were interviewed when the interviewers were available; thus, they represented a sample of convenience.

To determine whether *DSM-III* criteria for substance use disorders were met, subjects were questioned systematically by using the substance use section of the NIMH Diagnostic Interview Schedule (DIS) (5). To determine whether *DSM-III-R* criteria for substance use disorders were met, the substance use disorders section of the Structured Clinical Interview for *DSM-III*—Patient Version (6) was used. The two schedules were given in that order during the same interview, which took place on the inpatient unit 7–21 days after admission and as part of the initial intake process in the outpatient setting. Two postgraduate clinicians conducted all the interviews.

RESULTS

Characteristics of the Samples

In the inpatient unit, 22 (54%) of the 41 patients were men and 21 (51%) were white, 33 (80%) had a high school education or more, and their mean±SD age was 34±10 years. The numbers of patients with abuse of or dependence on substances according to *DSM-III* criteria were as follows: alcohol, 18 (44%); barbiturates, 10 (24%); cannabis, 10 (24%); stimulants, six (15%); opioids, 14 (34%); cocaine, 10 (24%); and hallucinogens, one (2%). Each patient could have more than one diagnosis. In the outpatient setting, 31 (74%) of the 42 patients were men and 26 (62%) were white, 34 (81%) had a high school education or more, and their mean±SD age was 29±7 years. The numbers of patients with abuse of or dependence on substances according to *DSM-III* criteria were as follows: alcohol, 23 (55%); barbiturates, six (14%); cannabis, seven (17%); stimulants, 14 (33%); opioids, 27 (64%); cocaine, 32 (76%); and hallucinogens, one (2%). Again, each patient could have more than one diagnosis.

As anticipated, the rates of substance use disorders were considerably higher in the outpatient sample, who identified themselves as substance abusers by seeking specialized treatment. For the three purposes of this study—to evaluate agreement between *DSM-III* and *DSM-III-R* criteria, to assess reasons for discrepancies between the two systems, and to assess the effect on agreement of requiring different numbers of criteria in *DSM-III-R*—the results from the two samples were nearly identical. Hence, for economy of presentation, the results for the combined samples will be presented here.

Agreement Across Diagnostic Systems

The agreement between diagnoses of substance use disorders made according to *DSM-III* and *DSM-III-R* criteria is shown in table 1. This table shows the number of patients on which the two systems agreed and diverged, the rate of patients receiving diagnoses, and the kappa coefficients of agreement (7). For the *DSM-III-R* criteria this information is given for when the minimum number of symptoms required was two, three, and four. Two trends are apparent from these findings. First, for the majority of drug categories the kappa coefficients were highest and the rates of diagnoses were most similar when the number of *DSM-III-R* criteria required was three or more. Second, when the cutoff point was three, the level of agreement between *DSM-III* and *DSM-III-R* was very high; the kappa coefficients were 0.79 or higher for all categories except hallucinogen abuse. Thus, the choice of three criteria as a cutoff point for the new criteria minimized changes in rates of disorders as well as the changes in the actual numbers of individuals receiving diagnoses.

An additional purpose of this field trial was to assess the reasons for any diagnostic discrepancies that might arise between the two systems. Overall, out of 581 diagnostic decisions shown in table 1, there were 28 (5%) disagreements between the two systems—six diagnoses were made by *DSM-III* exclusively and 22 diagnoses were made by *DSM-III-R* exclusively. Hence, with three or more criteria as the cutoff point, the new system tended to classify more individuals as having a substance use diagnosis in comparison with the old system. For the six instances in which a *DSM-III* diagnosis was made although *DSM-III-R* criteria were not met, there were two causes for disagreement: for three patients a diagnosis of dependence was made on the basis of tolerance without a pattern of pathological use and social dysfunction, and for three patients two criteria (one indicating drug-related social dysfunction and one indicating pattern of pathological use) were met by both systems, which was enough to qualify for abuse in *DSM-III* but not enough to qualify for dependence in *DSM-III-R*. For the 22 instances in which *DSM-III-R* diagnoses were made although *DSM-III* criteria were not met, the reasons were always due to the broader range of

TABLE 1. Agreement Between *DSM-III* and *DSM-III-R* in Diagnoses of Substance Abuse Disorder in 83 Patients

Met *DSM-III* Criteria	Met Two or More *DSM-III-R* Criteria				Met Three or More *DSM-III-R* Criteria				Met Four or More *DSM-III-R* Criteria			
	Yes	No	Rate (%)	κ[a]	Yes	No	Rate (%)	κ[a]	Yes	No	Rate (%)	κ[a]
Alcohol (49%)			58	0.83			49	0.90			43	0.78
Yes (N=41)	41	0			39	2			34	7		
No (N=42)	7	35			2	40			2	40		
Barbiturates (19%)			27	0.66			20	0.79			14	0.74
Yes (N=16)	14	2			14	2			11	5		
No (N=67)	2	59			3	64			1	66		
Cannabis (20%)			37	0.60			27	0.80			18	0.77
Yes (N=17)	17	0			17	0			13	4		
No (N=66)	14	52			5	61			2	64		
Stimulants (24%)			33	0.79			25	0.90			22	0.86
Yes (N=20)	20	0			19	1			17	3		
No (N=63)	7	56			2	61			1	62		
Opioids (49%)			54	0.88			49	1.00			48	0.98
Yes (N=41)	41	0			41	0			40	1		
No (N=42)	4	38			0	42			0	42		
Cocaine (51%)			58	0.81			54	0.88			48	0.86
Yes (N=42)	41	1			41	1			38	4		
No (N=41)	7	34			0	37			2	39		
Hallucinogens (2%)			12	0.31			8	0.42			6	0.56
Yes (N=2)	2	0			2	0			2	0		
No (N=81)	8	73			5	76			3	78		

[a]Agreement between diagnostic systems.

criteria in *DSM-III-R*, which denotes more specific behaviors indicative of dependence, and the fact that all nine of the criteria are in the same grouping rather than one each being required from different groupings (e.g., one symptom indicative of pattern of pathological use and one symptom indicative of social and occupational dysfunction). This latter cause for higher rates of diagnoses with *DSM-III-R* resulted mainly from the removal of social consequences as a requirement for making a diagnosis of a substance use disorder.

DISCUSSION

In this field trial of *DSM-III* and *DSM-III-R* criteria for diagnoses of substance use disorders, the effects of major changes in the diagnostic system did not bring about equivalent changes in the rates of diagnoses made in practice. When three criteria were used as a cutoff for making a *DSM-III-R* diagnosis, agreement between the two systems was high for all substances except for hallucinogens, for which *DSM-III-R* criteria yielded higher rates of dependence. In contrast with the concerns of some members of the diagnostic advisory group, the new system tended to be more likely than the old system to classify individuals as having a substance use disorder.

An assessment of the effect of changing the number of symptoms required to make a *DSM-III-R* diagnosis suggested the correctness of requiring three or more symptoms. Requiring fewer symptoms substantially raised rates of diagnoses and lowered agreement levels, and requiring more symptoms substantially lowered rates and agreement levels. The exception was hallucinogen dependence, for which raising the number of criteria increased agreement between the two systems by reducing the number of patients uniquely diagnosed by the new *DSM-III-R* criteria. It could be argued that the number of criteria should be raised for diagnosing hallucinogen dependence. However, inspection of the cases of newly diagnosed patients indicated that *DSM-III* may have been inadequately sensitive to subjects who used hallucinogens in a pathological way (used when socially inappropriate, preoccupied with use, had difficulty stopping) but who did not identify social consequences.

The overall impact of the new system was to increase the number of individuals meeting criteria for a substance use disorder. This occurred because of the removal of the requirement for social consequences to have occurred as a result of substance use and the increase in the number of behaviors considered indicative of loss of control of substance use. This result suggests that the new system may allow for a diagnosis earlier in the course of the disorder, before social consequences are manifest. The requirement of social consequences has been criticized on the grounds that these may depend more on the luck and the jurisdiction of the substance user than on the severity of his or her syndrome of substance use (1). In addition, requiring social consequences was believed to wrongly exclude individuals who had substantial but concealed use of psychoactive substances, such as a drug dealer who has not yet been identified by law enforcement officials or an addicted physician. In the few instances in which a *DSM-III* diagnosis was made although *DSM-III-R* criteria were not met, half were the result

of the weight placed on tolerance as a criterion, which has been criticized on the basis of imprecision and lack of specificity (1). In the other instances, the *DSM-III* diagnosis had been made on the basis of only two symptoms, indicating that the disagreement across systems was in the milder cases.

The high levels of agreement between the two diagnostic systems despite major differences in the conceptualization of the criteria suggest that the syndromes covered by substance use disorders may be sufficiently robust that they can be comparatively readily diagnosed in a variety of ways. Suggestions for criteria have emphasized many different aspects of excessive substance use, including use of large amounts and frequency of use, physical dependence and/or tolerance, social or medical consequences, or symptoms of diminished control over substance use (8). That different systems seem to yield similar diagnoses suggests that the different manifestations of substance use disorders coexist sufficiently that choice among the manifestations can vary widely but still capture the syndrome. Hence, as with the parable of the blind men and the elephant, the trunk and the massive sides or the tusks and the large legs are nonoverlapping but sufficiently distinctive criteria for "elephant"—they denote this type of animal if used as independent criteria. The issue of the relationship of the elements of a dependence syndrome to other ways of defining substance use disorders will be addressed in a future paper.

Given the relatively small number of subjects in this study and the use of treatment settings, the current findings must be seen as preliminary, although the similarity in high agreement levels at two very different treatment settings suggests that the findings of the current study would apply in other samples. However, replication of these findings with other populations is needed. Although the high level of agreement between the old and new systems may be seen as an indication that the old system did not need revision, it should be noted that the new system appears to detect substantial involvement with psychoactive substances before social consequences have occurred. Moreover, several other advantages of the new system include logical consistency across drug categories, greater ease in use due to the consistency of criteria across substances, ability to denote distinctions in severity of disorder, removal of excess emphasis on physiological aspects of dependence, and greater conceptual clarity with linkage to the hypothesized substance dependence syndrome (1).

SUBSEQUENT CHANGES IN *DSM-III-R*

Subsequent to the completion of this field trial, a redefined "abuse" diagnosis was reinstated in *DSM-III-R*, defined as follows:

A. A maladaptive pattern of substance use is indicated by at least one of the following: 1) continued use despite a persistent social, occupational, psychological, or physical problem that is caused or exacerbated by use of the substance, 2) recurrent use in situations when use is hazardous (e.g., driving while intoxicated).

B. Some symptoms of disturbance have persisted for at least 1 month or have occurred repeatedly over a longer period of time.

C. Patient has never met the criteria for psychoactive substance dependence for this substance.

This category was included to allow the diagnosis for those with comparatively mild disorders or who had only recently started to use a given type of psychoactive substance. It is conceived of as a residual category to be used only for those who have dysfunctional or hazardous substance use without other symptoms of dependence. On the basis of our field trial, we anticipate that this diagnosis will not be common because the overwhelming majority of substance users who met *DSM-III* criteria for abuse or dependence were found to meet *DSM-III-R* criteria for dependence.

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APPENDIX 1. Proposed *DSM-III-R* Criteria for Diagnoses of Substance Dependence Disorders

1. Repeated effort or persistent desire to cut down or control substance use.
2. Often intoxicated or impaired by substance use when expected to fulfill social or occupational obligations or when substance use is a hazard (e.g., does not go to work because hung over or high, goes to work high, drives when drunk).
3. Tolerance: need for increased amounts of substance in order to achieve intoxication or desired effect or diminished effect with continued use of same amount.
4. Withdrawal: substance-specific syndrome following cessation or reduction of intake of substance.
5. Frequent preoccupation with seeking or taking the substance.

6. Has given up some important social, occupational, or recreational activity in order to seek or take the substance.
7. Often uses a psychoactive substance to relieve or avoid withdrawal symptoms (e.g., takes a drink or diazepam to relieve morning shakes).
8. Often takes the substance in larger doses or over a longer period of time than he or she intended.
9. Continuation of substance use despite a physical or mental disorder or a significant social or legal problem that he or she knows is exacerbated by the use of the substance.

Current Need Versus Treatment History as Predictors of Use of Outpatient Psychiatric Care

Matthew J. Friedman, M.D., Ph.D., and Alan N. West, Ph.D.

The authors conducted a study of treatment utilization and outcome on a sample of 116 psychiatric outpatients at a Veterans Administration (VA) hospital. Utilization and outcome measures were obtained at a follow-up interview 18 months after a baseline assessment. Comparisons between patients with high and low rates of utilization revealed negligible relationships between use of services and severity of illness, clinical change, or demographics. However, previous use of VA outpatient and inpatient psychiatric services and VA psychiatric disability rating predicted utilization of psychiatric care during the study. The authors conclude that use of VA outpatient psychiatric care may reflect patients' help-seeking history more than their current clinical need.

(Am J Psychiatry 144:355–357, 1987)

The containment and reduction of medical costs have become increasingly imperative. Mounting pressures for fiscal restraint (1) have fostered the development of the diagnosis-related group (DRG) classification system (2) for the reimbursement of inpatient services. It is to be anticipated that a comparable reimbursement system will be applied eventually in the realm of outpatient psychiatry. It is necessary, therefore, to identify factors that influence utilization rates and hence costs for outpatient psychiatric services. To our knowledge, however, there have been few studies investigating the correlates of utilization rates in outpatient psychiatry.

Rates of utilization of outpatient psychiatric services may be related to several factors. A reasonable prediction, for example, is that patients who are more impaired initially will require more treatment sessions during a given time interval. Alternatively, limited clinical resources may be allocated to those patients with more promising prognoses. A third possibility is that utilization rates are unrelated to either initial severity of dysfunction or degree of improvement. Rather, utilization may reflect a stable behavioral characteristic that correlates across services (e.g., psychiatric services, medical services, or public financial assistance) and time intervals and is independent of the patient's clinical status.

We conducted a study to identify correlates of treatment utilization in a public outpatient psychiatric clinic. A sample of Veterans Administration (VA) psychiatric outpatients was assessed on a variety of measures, including demographics, diagnoses, and clinical outcomes, as well as utilization of all psychiatric and other hospital-based medical services before

Received Nov. 22, 1985; revised June 30, 1986; accepted Aug. 18, 1986. From the Psychiatry Service, Veterans Administration Hospital, White River Junction, Vt.; and the Departments of Pharmacology and Psychiatry, Dartmouth Medical School, Hanover, N.H. Address reprint requests to Dr. Friedman, Psychiatry Service (116A), VAMROC, White River Junction, VT 05001.

Supported by a Health Services Research and Development grant from the VA.

the study period. Each measure was examined for its relationship to current use of outpatient psychiatric care.

METHOD

Subjects were 116 veterans who had requested outpatient psychiatric care at the VA Hospital at White River Junction, Vt. This hospital serves a catchment area that includes all of Vermont and five counties of northern and western New Hampshire. At intake, the mean±SD age for the sample was 49.0±12.6 years, the mean annual income was $10,900±$9,400, and the mean number of years of education was 11.5±2.9. One hundred fourteen (98%) of the subjects were men, 70 (60%) were married, and all were white. Staff psychiatrists assigned the following diagnoses: depression, 53 (46%) of the patients; anxiety or neurotic disorder, 22 (19%); psychosis, 23 (20%); personality disorder, seven (6%); substance abuse, 27 (23%); and marital/situational adjustment problem, seven (6%). Some patients were assigned to more than one diagnostic category.

Subjects were recruited to participate in the study after an initial diagnostic evaluation for treatment planning. Following the provision of written informed consent, each patient responded to a structured interview administered by a trained interviewer. This initial interview assessed several content areas, including demographics, clinical history, and past use of supplemental income, medical, and psychiatric resources. It also yielded baseline levels for several measures of clinical outcome. Outcome measures assessed the capacity to be a self-supporting participant in the labor market, self-reported psychiatric symptoms, involvement with family members or friends, and abuse of alcohol or illicit drugs. The measure of symptoms was the Symptom Check List-90 (SCL-90) (3). The other measures were derived from a variety of sources, including the Denver Community Mental Health Questionnaire (4), the Intake Scale of the National Institute on Alcohol Abuse and Alcoholism (5), the Social Adjustment Scale (6), and the Psychiatric Status Schedule (7). Evidence for the reliability and validity of these outcome measures has been presented elsewhere (8). Outcomes were assessed again at a follow-up interview conducted 18 months after the initial interview. Utilization of VA psychiatric and medical care and use of non-VA mental health care were monitored during this 18-month study interval.

The number of VA outpatient psychiatric treatment sessions attended during the 18 months from intake to follow-up varied considerably across subjects. Fifty-one patients attended two, one, or no sessions during the study interval (mean±SD=0.8±0.9 sessions); these patients were classified as "low utilizers" of care. The remaining 65 patients attended at least three sessions (mean±SD=6.5±3.7 sessions); these patients were classified as "high utilizers" of care. Data analyses involved comparisons of high and low utilizers with respect to each intake and outcome measure.

RESULTS

Among the many variables considered, measures of previous use of services yielded the most consistent group differences. Compared with low utilizers of care, high utilizers had received outpatient psychiatric treatment for a mean of 5 months longer during the preceding 2 years ($t=2.95$, $df=114$, $p<.01$), had attended more VA outpatient psychiatric sessions during the preceding 18 months ($t=3.18$, $df=113$, $p<.01$), had made more outpatient visits to the VA alcohol rehabilitation program ($t=2.63$, $df=113$, $p<.01$), and had been hospitalized longer in the VA inpatient alcohol rehabilitation program ($t=2.47$, $df=113$, $p<.05$).

On the other hand, there were few group differences in the use of other health care services during the study interval. These services included inpatient VA psychiatric or medical care, outpatient VA medical care, or non-VA outpatient mental health care. The only significant difference indicated that high utilizers of VA psychiatric care also made more medical visits during the study ($t=2.13$, $df=114$, $p<.05$).

High utilizers were also more likely to have VA service-connected disability status ($\chi^2=10.75$, $df=1$, $p<.001$). The mean VA psychiatric disability percentage rating was higher for high utilizers (38.4%) than for low utilizers (16.6%) ($t=3.13$, $df=112$, $p<.01$). In addition, high utilizers were more likely to be diagnosed as depressed ($\chi^2=7.52$, $df=1$, $p<.01$) and somewhat more likely to be psychotic ($\chi^2=3.72$, $df=1$, $p<.06$). There were no other diagnostic differences between groups, nor did any significant demographic differences emerge.

Outcome measures assessed psychiatric symptoms, therapeutic goal attainment, employment status, reported frequency of use of alcohol or illicit drugs, monthly alcohol consumption, and social support through involvement with family or friends. Groups did not differ on the intake values of any outcome measure. Moreover, the only significant difference at the 18-month follow-up was for symptom change scores (i.e., the intake SCL-90 score minus the follow-up score). Low utilizers improved substantially from intake to follow-up, but there was little change for high utilizers ($t=1.98$, $df=88$, $p<.05$). The failure to observe more group differences is not attributable to unreliability in our outcome measures. Elsewhere (8) these measures have been shown to be sufficiently reliable to discriminate patients in different treatment settings.

In summary, high utilization of VA care during the study was related to greater previous utilization of VA psychiatric and substance abuse treatment and to greater chronicity as indicated by VA disability status. Utilization was generally unrelated to diagnostic or

demographic variables or to measures of adaptive functioning at the initial interview. Utilization was also largely unrelated to clinical outcomes.

DISCUSSION

Our results indicate that high utilizers of psychiatric care were more chronically psychiatrically disabled and had used more of a variety of mental health and other medical services in the past. On the other hand, treatment utilization was not related to demographics, symptoms, or clinical improvement. These findings suggest that treatment-seeking behavior was a stable characteristic in this population and that this behavior was not associated with current severity of illness or with the success of treatment.

Several caveats must be noted. It is unclear whether these findings may generalize to other public or private outpatient settings. In that regard it should be emphasized that although this VA hospital may treat more chronically ill and permanently disabled patients than other facilities, its outpatient psychiatric population consists of a fairly representative case mix. Chronically psychotic patients account for fewer than 20% of the patients. Furthermore, we obviously cannot say whether high and low utilizers differ on other characteristics not measured by our battery of tests (such as personality variables or capacity to cope with stress). Also, it is impossible to state whether clinical outcomes for high utilizers would have been less successful had their access to care been limited by their therapists.

These considerations notwithstanding, we have shown that a history of treatment seeking predicts utilization of outpatient psychiatric care better than does current clinical need. This finding warrants further investigation because it has important implications for the allocation of scarce psychiatric resources in the public sector.

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Male and Female Psychiatrists and Their Patients

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Data from a national survey were used to explore 1) whether the patients of male and female psychiatrists differed substantially in demographic or clinical characteristics and 2) whether there were any differences in psychiatrists' treatment of same-gender versus opposite-gender patients. Women constituted about two-thirds of the female but only one-half of the male psychiatrists' patient loads. Female psychiatrists tended to see all of their patients more frequently, but few other differences were found. Better educated patients of both genders tended to have same-gender therapists; patients experiencing marital disruption tended to be seen by therapists of the opposite gender. Implications of these differences for training and manpower development are discussed.

(Am J Psychiatry 1987; 144:358–361)

Over the last two decades, the proportion of psychiatrists who are female has risen from 12% to 19% (1)—a trend that is expected to continue. Thus, the next generation of psychiatric practitioners will include unprecedented numbers of women. At the same time, a heightened interest in gender-related professional issues has encouraged a wide range of reports on the experiences of women in psychiatry (2). Factors unique to the decision of women to pursue medicine as a career (3), psychiatric specialty training (4), and chief residency (5) have been described. Other studies have focused on the transition to active practice (6), the work and life patterns of female psychiatrists (7), and the role of women in academic psychiatry (8).

Presented at the 139th annual meeting of the American Psychiatric Association, Washington, D.C., May 10–16, 1986. From the Chestnut Lodge Research Institute; the American Psychiatric Association, Washington, D.C.; and the Department of Psychiatry, Yale University School of Medicine, New Haven, Conn. Address reprint requests to Dr. Fenton, Chestnut Lodge Research Institute, 500 West Montgomery Ave., Rockville, MD 20850.

Supported in part by grants from the Office of Education, American Psychiatric Association; and the Department of Psychiatry, Yale University School of Medicine; and by training grant MH-15783 from the National Institute of Mental Health.

The authors thank Linda Beth Berman for editorial assistance and Martha Teitelbaum, Ph.D., Gary Tischler, M.D., Thomas H. McGlashan, M.D., and Dexter M. Bullard, Jr., M.D., for manuscript review and support.

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Most reports describe potential obstacles to women's professional achievement in terms of sex role stereotyping, traditions within the medical hierarchy, and strains arising from balancing professional and family obligations. Consistent with these observations, comparative empirical studies have found that female psychiatrists are less often Board certified, work fewer hours per week, and tend to fill less prestigious positions in institutional settings than their male counterparts (7, 9, 10).

Although it has been suggested that the patients seen by female psychiatrists differ from those seen by men, to our knowledge no study has explored the relation between psychiatrists' gender and the populations of patients served. If substantial differences do exist, they may have important implications for education and delivery of services as the ratio of male to female psychiatrists continues to shift. In this report we use data from a national sample of psychiatrists to explore differences in practice activities. Specifically, two questions were asked: 1) Do the patients of male and female psychiatrists differ in terms of demographic or clinical characteristics? 2) Are there any differences in psychiatrists' treatment of same-gender versus opposite-gender patients—for example, in female psychiatrists' treatment of male and female patients?

METHOD

This study used a randomly selected sample of psychiatrists, both members and nonmembers of the American Psychiatric Association, drawn from the APA master file during the summer of 1979. Data were obtained from 307 psychiatrists—a response rate of 66% of those who received the survey material. On the basis of information from the APA master file, we found no significant differences between respondents and nonrespondents.

Respondents were asked to provide detailed demographic, diagnostic, and treatment data on each of the next 10 patients they saw after receiving the survey material. Since *DSM-III* had not been officially adopted at the time of the survey, *ICD-9* diagnostic categories were used. Excluding residents and retired practitioners, 221 male and 44 female practicing psychiatrists provided data on 1,927 and 384 patients, respectively. The design and sampling procedures of the study and the practice activities of these psychia-

trists have been previously described (11).

Most of the psychiatrist respondents were white (91% of the men; 86% of the women); the mean±SD age of each group was 48±10.5 years. Male psychiatrists were significantly more likely to be graduates of American medical schools (85% versus 72%; $\chi^2=4.23$, df=1, $p<.05$), to have been born in the United States (84% versus 65%; $\chi^2=8.76$, df=1, $p<.005$), and to be Board certified (68% versus 47%; $\chi^2=7.51$, df=1, $p<.005$). Female practitioners more frequently worked part-time (25% versus 6%; $\chi^2=14.24$, df=1, $p<.0002$) and hence, as a group, worked fewer total hours per week (41 versus 49 hours; t=2.95, df=206, $p<.005$).

RESULTS

Practice Activities

Employment in inpatient psychiatric hospitals, general hospitals, and state or federally operated facilities accounted for 42% of all hours worked by female psychiatrists, compared to 26% of the hours worked by male psychiatrists. The men spent a greater proportion of their professional time in private practice (42% versus 32%) and university settings (9% versus 5%). Psychiatrists of each sex reported that about 21% of their hours were spent in outpatient clinics and other settings.

Direct patient care was the major activity for psychiatrists of both genders (men, 65%; women, 61%). Each group spent about 10% of their time in consultative activities and 8% in teaching. Women spent a greater proportion of their time in administrative activities (20% versus 14%) and a smaller proportion in research (1% versus 3%).

Characteristics of Patients

Table 1 displays characteristics of the psychiatrists' 10 consecutive patients. The most consistent finding was the high proportion of female patients in both the inpatient and outpatient practices of the female psychiatrists. In addition, female psychiatrists treated a greater proportion of members of minority groups as inpatients. The marital status and family income level of the patients were comparable, but the female psychiatrists' outpatients had a significantly lower level of educational achievement. Consistent with the practice setting data, a greater proportion of the female psychiatrists' patients were inpatients in state hospitals and outpatients at general hospitals.

No significant differences between male and female psychiatrists were found in relation to diagnosis, prescription of psychotropic medications, or previous inpatient hospitalization of patients. In both inpatient and outpatient settings, however, female psychiatrists were more likely to see their patients at intervals of at least once a week. Female psychiatrists saw a smaller proportion of inpatients for evaluation, although a larger proportion of these inpatients were being seen for the first time.

Practitioners' Same- and Opposite-Gender Patients

Differences between psychiatrists' same- and opposite-gender patients were explored by focusing on private practice as the setting in which value-linked treatment practices might be most evident. Male and female psychiatrists' same-gender and opposite-gender patients were compared along each variable in Table 1. We used the chi-square statistic, adjusted to a p value of .01 for multiple hypothesis testing (12), to determine whether differences were significant.

Three differences emerged between the male practitioners' male (N=512) and female (N=573) private office patients. Female patients were more likely to be experiencing marital disruption (25% versus 16% divorced; $\chi^2=17.7$, df=2, $p<.0001$) and to have a diagnosis of neurosis (45% versus 35%; $\chi^2=20.1$, df=4, $p<.0005$). The male psychiatrists' male patients were more likely to have attended college (67% versus 58%; $\chi^2=60.0$, df=7, $p<.0001$).

Female psychiatrists' female patients seen in private practice (N=124) were more likely than their male patients (N=56) to have attended college (63% versus 55%; $\chi^2=21.7$, df=7, $p<.005$). Although 21% of the female practitioners' male patients and 15% of their female patients were widowers or divorced, the difference was not statistically significant.

DISCUSSION

The practices of female psychiatrists differed in several ways from those of male colleagues. Consistent with findings in previous studies, female psychiatrists spent a greater proportion of their time in settings based in organizations and were less involved in academia and private practice. The most notable difference was the predominance of female patients in the practices of female psychiatrists—a finding not unique to psychiatry. Comparable percentages of patients have been reported for female practitioners in family practice/internal medicine and in psychiatry (13). Studies of patients' preferences have found that women are between one and one-half and three times as likely to prefer a female physician (14–19), particularly when a woman is perceived as a more credible provider, e.g., in obstetrics/gynecology, family planning, and psychotherapy (16). A relatively small preference for a same-sex physician results, over time, in the physician's accrual of a high percentage of same-sex patients (17). The paucity of female physicians (compared with female patients) may result in a greater demand for their services, as reflected by the number of days a patient must wait for an appointment and by the fees charged (14). In agreement with Seiden (18, 19), we believe that these findings point to the presence of

TABLE 1. Sociodemographic and Clinical Characteristics of Male and Female Psychiatrists' Inpatients and Outpatients

Item	Inpatients of Male Psychiatrists (N=384)		Inpatients of Female Psychiatrists (N=105)		Outpatients of Male Psychiatrists (N=1,543)		Outpatients of Female Psychiatrists (N=279)	
	N	%	N	%	N	%	N	%
Treatment setting								
Private office	29	8	4	4[a]	1086	70	180	65[a]
General hospital	161	42	45	43	66	4	49	18
Private hospital	68	18	4	4	12	1	2	1
State hospital	54	14	38	36	17	1	0	
VA hospital	31	8	0		48	3	0	
Community Mental Health Center	9	2	9	9	155	10	29	10
Other	32	8	5	5	159	10	18	6
Female sex	182	47	73	70[a]	786	51	180	65[a]
White race	329	86	76	73[a]	1361	88	242	87
Marital status								
Married	102	27	24	23	659	43	126	45
Widowed/divorced/separated	98	26	27	26	347	23	45	16
Never married	179	47	54	51	532	35	108	39
Annual income								
<$10,000	184	53	42	54	447	30	84	32
$10,000–$15,000	65	19	12	15	321	21	50	19
$15,000–$25,000	61	17	12	15	321	21	54	21
$25,000–$50,000	27	8	6	8	246	16	41	16
>$50,000	12	3	6	8	174	12	34	13
Education								
Grades 0–8	70	19	31	30	161	11	48	17[b]
Grades 9–11	99	27	27	26	191	13	35	13
High school graduate	111	30	27	26	379	25	54	19
Some college	66	18	13	13	466	31	98	35
College/graduate degree	26	7	6	6	326	21	42	15
Source of payment								
Personal funds (100%)	49	13	14	14	591	39	110	40
Some third party funding	327	87	85	86	924	61	162	60
Diagnosis								
Schizophrenia	108	28	28	27	222	14	29	10
Organic mental disorder	34	9	20	19	31	2	4	1
Major affective disorder	53	14	10	10	130	8	29	10
Neurosis	63	16	10	10	534	35	98	35
Character disorder	34	9	5	5	301	20	57	21
Other	92	24	31	30	324	21	61	22
Treatment								
Evaluation	125	33	25	24[b]	245	16	49	18
Dynamic/individual therapy	60	16	15	14	574	37	120	43
Psychoanalysis	9	2	0		108	7	8	3
Supportive individual	91	24	34	33	333	22	57	21
Medication check	33	9	6	6	130	8	21	8
Family/group therapy	9	2	10	10	109	7	18	6
Other	49	13	14	14	32	2	5	2
Received medication	298	79	77	73	726	48	128	46
Frequency of treatment								
Less than once a week	43	17	5	7[c]	532	39	67	28[d]
Once a week	38	15	16	24	526	39	118	49
More than once a week	175	68	46	69	290	22	58	24
Previous hospitalization	297	80	86	83	487	32	79	28
Previous psychiatric treatment	154	40	23	22[b]	1067	69	195	70

[a]Significant difference between groups, p=.0001.
[b]Significant difference between groups, p=.0005.
[c]Significant difference between groups, p=.05.
[d]Significant difference between groups, p=.005.

substantial opportunities for women in clinical practice at a time when competition and changes in reimbursement patterns place constraints on the profession at large.

The settings in which a psychiatrist works determine in part the characteristics of his or her patients. Thus, female psychiatrists' greater involvement in public settings is related to the overrepresentation of minorities and less well educated individuals among their patients. These differences are not significant when private practice alone is considered. Of interest is female psychiatrists' greater tendency to see their pa-

tients once a week or more often—in spite of the fact that they work in settings associated with a lower intensity of physician-patient contact. Female physicians in other specialties also spend more time in face-to-face contact with their patients (13, 14). While it is tempting to ascribe this tendency to the well documented finding that female medical students and physicians are more highly oriented toward interpersonal relationships and affectivity in medical practice (20), it must also be noted that men are more likely than women to work in private fee-for-service settings in which income depends on the number of patients seen (21).

Comparison of same- and opposite-sex dyads calls into question some long-held assumptions. Contrary to the finding of at least one study (13), female patients in our study were not prescribed psychotropic medications with greater frequency than male patients. Although female patients of the male psychiatrists were more likely to be given a diagnosis of neurosis, this was also true for the female patients of the female psychiatrists (41% of their women patients versus 36% of their male patients). The extent to which this reflects differences in physicians' labeling or patients' help seeking and utilization behavior is unknown.

Two unexpected but intriguing cross-sex differences were noted. Both male and female psychiatrists' opposite-gender patients were more likely to be widowed, divorced, or separated. Might efforts to replace the lost object play a role in the choice of (or continuation with) a psychiatrist by patients experiencing marital disruption and loss? Contrariwise, more highly educated, and thus perhaps more sophisticated, patients were slightly more likely to have a same-gender psychiatrist.

It should be noted that the profiles of patients described here are from the perspective of a short period of time—10 consecutive patients. Because of this, patients seen at infrequent intervals tend to be underrepresented (22). However, while the findings do not reflect the entire universe of patients seen by the respondents, the results are valid in comparing the activities of two groups of practitioners.

The comparison suggests to us that, by and large, a medical practice is a medical practice and that the similarities between the patients of male and female psychiatrists outweigh the differences. Manpower estimates do not require adjustment because female practitioners are seeing an unrepresentative or narrow spectrum of patients. It is clear, however, that after graduation, female residents will be likely to spend a substantial portion of their professional time treating women. The relative paucity of women in academic and teaching roles becomes increasingly problematic as the number of women seeking training in psychiatry increases.

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Short-Term Course of Depressive Symptoms in Patients With Eating Disorders

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After inpatient treatment focused on aberrant eating behavior, six depressed normal-weight bulimic patients showed little improvement in depressive or eating symptoms. Four depressed anorexic patients with bulimic behavior improved in both areas, and five restricting anorexic patients had an intermediate response.

(Am J Psychiatry 1987; 144:362–364)

Depressive symptoms and eating disorders appear to be associated (1, 2). Question remains about whether eating disorders are variants of depressive disorders or depressive symptoms occur secondary to eating disorders. Prior studies, relying on cross-sectional diagnoses of affective illness in acutely ill patients with eating disorders, have not convincingly differentiated syndromal depression from dysphoric affect given the overlapping diagnostic criteria for depression and eating disorders (3). Following these depressive features over time could clarify this association, but few such studies have been undertaken.

Cantwell et al. (4) found that 44% of individuals previously hospitalized with anorexia nervosa met the Feighner criteria for an affective disorder at follow-up (mean=4.9 years). In a 2–5-year follow-up of 30 previously hospitalized bulimic patients, Swift et al. (5) found that none met the Research Diagnostic Criteria (RDC) (6) for definite major depressive disorder, despite persistence of bulimia in 87%. In this paper we present preliminary findings from a study assessing the short-term course of depressive symptoms in hospitalized patients with eating disorders.

METHOD

Eighteen female inpatients were recruited from a university hospital inpatient unit that specializes in behavioral management of eating disorders. While adjuvant individual, group, and family therapy is offered, the therapeutic focus is not on depressive illness (7). No patients received psychoactive medication during their inpatient eating disorder treatment, although patients 9 and 16 began antidepressant regimens before follow-up.

Table 1 lists characteristics of the women. Nine met the *DSM-III* criteria for anorexia nervosa, while eight met the *DSM-III* criteria for bulimia and were within 15% of ideal body weight at admission. The anorexic patients were divided into two subgroups: restricting (N=5), those who lost weight solely by dieting, and bulimic (N=4), those who dieted, binged, and purged. One patient with normal-weight bulimia left the hospital before completing the protocol and was omitted from the data analyses. Informed consent was obtained from all participants and from the parents of those under age 16.

Each participant completed a Schedule for Affective Disorders and Schizophrenia (SADS) interview (8), the 17-item Hamilton Rating Scale for Depression (9), and the Beck Depression Inventory (10) during the first week of hospitalization, the Hamilton and Beck scales at discharge and 1-month follow-up, and the SADS-Change interview at discharge. The anorexic patients

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Supported by grants from the Research and Development Fund, Department of Psychiatry, University of Wisconsin Medical School, and by NIMH grant MH-17139.

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TABLE 1. Depressive Symptoms of Anorexic and Bulimic Women Before and After Behaviorally Focused Treatment

Patient	Age (years)	RDC Major Depressive Disorder		Hamilton Depression Score			Beck Score			Follow-Up Eating Behavior
		Admission	Discharge	Admission	Discharge	Follow-Up	Admission	Discharge	Follow-Up	
Anorexia nervosa										
Bulimic behavior										
1	17	Definite	Definite	26	10	9	36	18	3	Good
2	15	Definite	None	21	4	3	25	8	9	Good
3	16	Probable	None	19	9	3	35	0	9	Good
4	16	Definite	None	21	2	10	23	0	11	Poor
Restricting behavior										
5	18	Definite	None	18	8	16	30	3	7	Poor
6	17	Definite	None	27	3	9	27	12	16	Good
7	33	Definite	None	23	3	13	22	18	22	Poor
8	14	Definite	None	21	5	16	45	19	10	Poor
9	15	Probable	None	8	3	19	24	6	22	Good
Normal-weight bulimia										
10	17	None	None	6	4	10	9	9	2	Good
11	24	Definite	None	22	7	27	13	1	7	Poor
12	21	Definite	Probable	16	14	15	16	7	15	Poor
13	16	Definite	None	30	3	0	31	4	3	Good
14	22	None	None	4	4	4	0	0	1	Good
15	20	Definite	None	21	8	8	25	8	19	Poor
16	22	Definite	Definite	20	18	12	35	36	20	Poor
17	17	Probable	None	14	7	12	20	25	27	Poor

were discharged after a mean±SD of 5.5±1.1 weeks, and the normal-weight bulimic patients were discharged after 3.5±0.8 weeks.

The RDC diagnoses of current major depressive disorder are shown in table 1. To be assigned a diagnosis of depression at admission, a patient had to have a Hamilton score of at least 14 or a Beck score of at least 20. The criteria for remission of depression at follow-up were a Hamilton score less than 7 and a Beck score less than 10. Good eating behavior outcome was defined for each group: 1) restricting anorexic patients, weight gain of over 2.5 kg since admission; 2) bulimic anorexic patients, weight gain of over 2.5 kg since admission *and* vomiting less than twice a week; and 3) normal-weight bulimic patients, vomiting less than twice a week. Eating behavior was monitored by ward staff members, who provided detailed daily reports in the patients' hospital charts.

RESULTS

At admission all nine anorexic patients were rated as depressed on at least one measure. By discharge six showed remission of their initial depression. Each weighed at least 2.5 kg over her admission weight, and all of the bulimic anorexic patients had ceased vomiting. At follow-up, although five did not meet the admission criteria for depression, only two continued to meet the remission criteria (both were bulimic anorexic). All bulimic anorexic patients showed marked declines in depressive symptoms (mean±SD decline: Hamilton=15.5±3.1, Beck=21.8±9.5); the restricting anorexic patients showed more variability and less overall improvement (mean±SD decline: Hamilton=4.8±10.7, Beck=14.2±13.2). Three of the four bulimic anorexic patients demonstrated good eating behavior, as opposed to two of the five restricting anorexic patients.

Six of the eight normal-weight bulimic patients were depressed on admission. At follow-up only one of these six (patient 13) met the criteria for remission (mean±SD decline: Hamilton=5.6±11.5, Beck=6.9±10.7), four still met the admission criteria for depression, and only one (patient 13) showed good eating behavior. The two normal-weight bulimic patients who were not depressed at admission reported good eating behavior at follow-up.

DISCUSSION

The course of depressive symptoms varied among the eating disorder groups. Most striking was the finding that the normal-weight bulimic patients who were depressed initially improved little in either depressive or eating symptoms after inpatient treatment focused on eating behavior. Conversely, the anorexic patients with concurrent bulimic behavior showed significant reduction in both eating and depressive symptoms with this treatment. The response of both symptom domains in restricting anorexic patients was intermediate. While tempered by the small sample, our data suggest that the etiology, course, and appropriate treatment of depressive symptoms in bulimic patients may differ depending on the presence or absence of significant weight loss. The relationship between depression and eating disorders appears complex: neither the primary nor the secondary affective disorder hypothesis alone can account for our data. Further

longitudinal study of depressive symptoms in patients with eating disorders is recommended.

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APA Periodicals Office at the 1987 Annual Meeting

The office of the three APA periodicals, the *American Journal of Psychiatry, Hospital and Community Psychiatry,* and *Psychiatric News,* will be in room L-12 in the Chicago Convention Center. The office will be open Sunday, May 10, 10:00 a.m.–5:00 p.m., and Monday–Thursday, May 11–14, 8:00 a.m.–5:00 p.m.

The *American Journal of Psychiatry* does not have first refusal rights for any papers presented at the annual meeting. However, the *Journal* welcomes the submission of annual meeting papers, which should be in final form and conform to the requirements in "Information for Contributors" (in most issues and available on request). Questions should be directed to the *Journal*'s editorial office at APA (202-682-6020).

Hospital and Community Psychiatry welcomes the submission of material from the annual meeting. The journal publishes clinical, research, and administrative material of interest to professional staff members in mental health facilities and agencies. Papers may be submitted singly, or papers from symposia or paper sessions may be submitted as a group for consideration as a special section. Material must be in final form, ready for blind peer review, and must be in an electronically scannable typeface. Details are given in *H&CP*'s "Information for Contributors," published in the January 1987 issue, and are available from the *H&CP* editorial office at APA (202-682-6070).

Staff of both journals will be available to answer authors' questions. Both journals publish only original material that has not been published elsewhere in any form and that is not being considered for publication elsewhere. Four copies are required for either journal.

The staff of *Psychiatric News* will meet daily in the office to discuss news coverage of the meeting. Persons who wish to contact members of the staff may leave messages to arrange appointments or may leave written announcements or letters for possible publication in the newspaper.

Prevention of Episodic Water Intoxication With Target Weight Procedure

Morris Benjamin Goldman, M.D., and Daniel Jonathan Luchins, M.D.

An effective, practical, and inexpensive method of preventing water intoxication in inpatients is described. The procedure uses the relationship between acute changes in body water and body weight to predict body weights associated with severe hyponatremia.

(Am J Psychiatry 1987; 144:365–366)

Water intoxication occurs in 3%–5% of chronically hospitalized psychiatric patients (1, 2). This syndrome is characterized by profound hyponatremia (serum sodium level<120 meq/liter) and a variable constellation of neurologic symptoms, including delirium, seizures, coma, and death. While specific, reversible factors are occasionally found, the usual recommendation is to restrict fluid intake. Unfortunately, this is rarely feasible on a psychiatric ward (3, 4). While other measures have been suggested (2, 4–7), none has been shown to reduce the incidence of the syndrome.

We modified a water intake regimen that has been used to prevent water intoxication and dehydration in patients with adipsic hypernatremia (8). The procedure is simple and relies on the relationship between acute changes in body water and body weight.

METHOD

Patients with histories of water intoxication were identified by reviewing records of transfers from a chronic state hospital to medical facilities for acute medical care. Only conditions that included 1) a clinical presentation of seizures or coma and 2) an admission serum sodium level of less than 120 meq/liter which 3) could not be accounted for by medical illness or medication were counted as episodes of water intoxication. During the 16-month period before the study (during which these data had been recorded), eight subjects suffered 16 episodes (see table 1). These episodes were evenly divided between the two 8-month periods and resulted in 83 days of care in medical facilities.

Baseline weights and simultaneous serum sodium concentrations were obtained twice a week for 2 weeks while the eight patients were not water intoxicated. The mean serum sodium level (MSS) and mean body weight (MBW) were calculated and then used to predict a body weight at which the serum sodium level would be significantly lower than at baseline but not yet at a level associated with water intoxication. We chose a minimum allowable sodium level (MAS) of 125 meq/liter for patients whose mean serum sodium level was 132 meq/liter or higher. For those whose mean serum sodium level was less than 132 meq/liter, the minimum allowable level was the mean serum sodium level minus 7 meq/liter. It was assumed that patients who were chronically hyponatremic could tolerate lower sodium concentrations (9). The weight associated with this minimum allowable sodium level, the maximum allowable body weight, was calculated by using the following simple theoretical relationship:

$$\text{Maximum allowable body weight} = \text{MBW} \times (\text{MSS}/\text{MAS})$$

The calculated maximum allowable body weight was 2.5–5.5 kg above the mean body weight.

The patients were kept on their original units and maintained on their previous neuroleptic doses. No new medications known to influence water balance were prescribed. A 30-minute session was held with the nonnursing staff to explain the procedure and instruct them in identifying prodromal signs of water intoxication (ataxia, confusion, vomiting, tremor) (9). Informed consent was obtained from the patients after the procedure was explained to them.

The patients were weighed three times each week and whenever staff observed prodromal signs. If the weight exceeded the maximum allowable body weight,

Presented in part at the 138th annual meeting of the American Psychiatric Association, Dallas, May 18–24, 1985. Received May 8, 1986; revised Sept. 15, 1986; accepted Oct. 31, 1986. From the Department of Psychiatry, University of Chicago Medical Center. Address reprint requests to Dr. Goldman, Department of Psychiatry, University of Chicago Medical Center, 5841 South Maryland, Chicago, IL 60637.

Supported in part by the Brain Research Foundation, an affiliate of the University of Chicago, and by Geriatric Mental Health Academic Award MH-00564 from NIMH to Dr. Luchins.

The authors thank Ian Aitken, M.B.A., Solomon Noguera, M.D., Paul Shyve, M.D., and the staff of Manteno Mental Health Center, Manteno, Ill., for their assistance and Gary L. Robertson, M.D., Richard L. Landau, M.D., Ned Weiss, M.D., and Robert Gibbons, Ph.D., for their reviews of the manuscript.

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TABLE 1. Sodium Levels of Eight Patients With Previous Water Intoxication Who Exceeded Maximum Allowable Weights

Patient	Prior Episodes	Months in Study	Statim Sodium Measurements (after findings of excess weight)	Sodium Level Below Allowable Minimum	
				Instances	Level (meq/liter)
1	1	10	2	0	
2	3	10	2	1	115
3	1	10	2	0	
4	3	10	6	2	123, 117
5	1	9	9	2	124, 123
6	2	10	2	1	121
7	4	2	1	1	118
8	1	6	2	0	
Total	16		26	7	
Mean	2	8.3	3.3		120.2
SD	1.2	2.7	2.5		3.4

the patient's sodium level was determined within 2 hours. If the value was less than the minimum allowable sodium level, the patient was placed in seclusion for 24 hours. The patient was not restrained and was permitted to eat, drink small amounts, and smoke. The patient was weighed every 8 hours on the day after release and then returned to the prior schedule.

The frequencies of water intoxication before and during the study were compared by means of a Poisson distribution (10). Weights and sodium levels were measured simultaneously every other week to determine the relationship between changes in serum sodium level and body weight by means of standard linear regression.

RESULTS

No patient showed signs of water intoxication during the study, a significant difference from the frequency before the study ($\chi^2=7.71$, df=1, $p<.01$) (10). The subjects exceeded their maximum allowable body weights on 26 occasions (see table 1). All but two of the elevated body weights were found during routine weighings. In seven instances the resulting sodium concentration was below the minimum allowable and the patient was placed in seclusion (see table 1). The patients' weights were a mean±SD of 4.2±1.5 kg above their initial mean body weights in these seven instances. During the water restriction the patients lost an average of 7.1±2.4 kg.

The correlation coefficient between change in body weight and serum sodium level was $r=-.74$ ($N=110$). The mean sodium level did not differ significantly between the study period and baseline (129.5±2.9 versus 127.9±3.8 meq/liter; paired $t=.95$, n.s.).

DISCUSSION

The data indicate that water intoxication can be prevented by monitoring changes in body weight and imposing water restriction when sodium levels drop precipitously. The procedure was cost effective and saved about $25,000 in medical expenses. We have since reduced the time patients spend in isolation from 24 to 16 hours, and in the subsequent 12 months, with the same procedure otherwise, no episodes have occurred. The correlation of $r=-.74$ between change in weight and serum sodium level confirms that large drops in sodium concentration are likely to be accompanied by significant increases in body weight. The fact that the mean serum sodium levels remained low and were not altered by the study suggests the results are probably not due to nonspecific effects on water intake. The program was carried out on five units of a state mental hospital without the addition of new staff and with once-weekly supervision by a psychiatrist. It may be adaptable to comparable clinical settings.

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Predictors of Interepisode Symptoms and Relapse in Affective Disorder Patients Treated With Lithium Carbonate

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Ann Schlegel, R.N., and Ngaere Baxter, Ph.D.

For 98 affective disorder patients receiving lithium prophylaxis for a mean of 45 months, number of interepisode symptoms correlated with relapse rate. Response to prophylaxis appeared highly determined by prelithium frequency of episodes and duration of lithium treatment.

(Am J Psychiatry 1987; 144:367–369)

Discussion of the diagnosis of bipolar and unipolar affective states in standard textbooks is limited to actual episodes of mania and depression. No "residual" affective condition is specified, and there has been little research on the quality of functioning between episodes.

We hypothesized that patients who exhibit greater mood fluctuations and more affective symptoms between episodes would also have more relapses. Further, we hypothesized that there would be an association between fewer interepisode symptoms and factors associated with better lithium response (defined as lower relapse rate)—bipolar illness (1), family history of bipolar illness and lithium response (1), and three or fewer episodes per year (2). The relationship between lithium plasma level and interepisode state is unclear (3–5); our own preliminary data (5) showed no relationship between interepisode symptoms and lithium level. In view of our previous finding that a minimum of 6 months is required to ascertain the efficacy of lithium prophylaxis (6), we predicted that longer duration of lithium therapy would be associated with better response, defined as either lower relapse rate or fewer interepisode symptoms.

Presented in part at the IV World Congress of Biological Psychiatry, Philadelphia, Sept. 8–13, 1985, and the World Psychiatric Association Regional Symposium on Affective Disorders, Athens, Oct. 13–17, 1985. Received June 21, 1985; revised July 7, 1986; accepted Nov. 13, 1986. From the Department of Lithium Studies, New York State Psychiatric Institute; and the Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York. Address reprint requests to Dr. Goodnick, Department of Lithium Studies, New York State Psychiatric Institute, 722 West 168th St., New York, NY 10032.

Supported in part by Mental Health Clinical Research Center grant MH-30906 from NIMH.

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METHOD

We studied 98 patients admitted to a specialized lithium outpatient clinic with histories of primary affective disorder (7). Patients with histories of hospitalization for mania were labeled bipolar I (N=54) (8). Patients with histories of hospitalization for depression and outpatient treatment for mania were labeled bipolar II (N=27). Patients who received outpatient treatment only for mania and depression were labeled bipolar, other (N=10). Patients without mania or hypomania were labeled unipolar or unipolar, other, depending on whether they received inpatient treatment (N=7). There were 46 men and 52 women; their mean±SD age was 49.3±14.7 years. All patients gave informed consent for participation in this study.

On the basis of weight, age, medical status, and acquiescence, each patient was given a prophylactic lithium dose of 600–1500 mg/day, which was maintained throughout the course of treatment. The patients were treated for 44.6±20.4 months, and their overall blood lithium level was 0.71±0.14 meq/liter. The deviation from the mean level was calculated for each patient, and the mean of the values for all patients was 0.11 meq/liter.

During prophylactic care, at each visit (approximately monthly) each patient completed a systematic record of 11 possible symptoms of mania, 32 possible symptoms of depression, and 18 possible side effects. In addition, the patient made a mood rating on a 7-point scale (extreme mania=7, normal=4, extreme depression=1). Before lithium treatment, 22 patients had had fewer than one affective episode per year, 36 had had one per year, 26 had had two or three per year, and seven had had four or more per year. For 51 patients the age at onset was 29 years or younger, for 21 it was 30–39 years, and for 24 it was 40 years or older. Thirty-two patients had family histories of bipolar disorder, and 28 had family histories of unipolar disorder. Relapse during the course of treatment was defined as the fulfillment of the Feighner criteria for mania or depression (7).

Several dependent variables were used to characterize the interepisode status of each subject. To exclude early symptoms of a forthcoming relapse from assessment of the interepisode period, we omitted from the

TABLE 1. Effect of Pretreatment Episode Rate on Response to Lithium for 91 Patients With Affective Disorder

Episodes Per Year Before Treatment	Depressive Symptoms Per Visit		Side Effects Per Visit		Mood Shifts Per Visit		Manic Relapses Per Month in Bipolar I Patients	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
<1 (N=22)	0.31	0.51	0.57	0.42	0.14	0.18	0.017	0.032
1 (N=36)	0.38	0.57	0.42	0.42	0.13	0.21	0.016	0.025
2 or 3 (N=26)	0.31	0.48	0.49	0.53	0.08	0.13	0.014	0.043
≥4 (N=7)	1.15[a]	1.43	0.88	1.07	0.23	0.25	0.035	0.031

[a]Significantly higher than for other patient groups (F=3.58, df=3, 87, p=.02).

calculations the last visit (a minimum of 1 month) before the one at which the criteria for mania or depression were met. A symptom rate for each patient was obtained by averaging the number of symptoms reported per visit over the entire period of lithium treatment. A side effect rate was calculated likewise. As an index of mood lability between episodes, a mean "mood shift" value was determined from the physician's rating. The absolute deviations from the normal mood rating of 4 (the deviation of both 5 and 3 would be 1) were averaged over all visits. A relapse rate was determined by dividing the number of relapses by the number of months that the patient received treatment. This led to an apparently low rate of relapse—0.030 per month for manic and depressive relapses combined. However, this corresponds to a yearly relapse rate of 20%–40%.

These dependent measures were examined in relation to eight possibly relevant variables: diagnosis, age, sex, prelithium episode rate, age at onset of illness, family history of affective disorders, mean lithium level, and duration of lithium treatment.

RESULTS

Neither age nor sex was related to any measure of interepisode symptoms or relapse. Bipolar I patients had the highest rate of manic symptoms, followed by bipolar, other, and bipolar II patients. The analysis of variance for the three bipolar groups only just missed significance (F=2.81, df=2, 88, p=.06). The differences among the diagnostic groups in depressive symptoms per visit, mood shifts per visit, side effects per visit, and relapse rate were not significant.

The patients who were between 30 and 39 years of age at onset had the lowest rate of mood shifts, but this difference did not reach significance (F=2.49, df=2, 92, p=.09). Age at onset was not significantly related to any other dependent measure.

The patients with four or more relapses per year before lithium treatment had a significantly higher mean number of depressive symptoms per visit than patients with less than one, one, and two or three episodes per year (F=3.58, df=3, 87, p=.02) (see table 1). These rapid cyclers also had the highest mean number of mood shifts per visit and the highest rate of manic relapses among bipolar patients, but the differences were not significant according to analysis of variance (to keep severity of illness consistent, the data on manic relapses were confined to bipolar I patients).

The rates of interepisode symptoms, side effects, and relapse were not significantly associated with family history of affective disorder in general and bipolar disorder in particular or with mean lithium level. Duration of lithium treatment was significantly correlated with many factors: mean number of manic symptoms per visit ($r=-.35$, $p<.001$), mean number of mood shifts per visit ($r=-.35$, $p<.001$), rate of manic relapse ($r=-.32$, $p<.001$), and rate of depressive relapse ($r=-.19$, $p=.03$). Thus, a patient had fewer symptoms between episodes and a smaller chance of relapse the longer he or she continued to take lithium.

Patients reporting more symptoms and less mood stability were more likely to also show complete relapse into depression or mania. Mean number of mood shifts per visit correlated significantly with both rate of manic relapse ($r=.56$, $p<.001$) and rate of depressive relapse ($r=.58$, $p<.001$). Number of manic symptoms reported per visit correlated strongly with manic relapse rate ($r=.71$, $p<.001$), and number of depressive symptoms reported per visit correlated with depressive relapse rate ($r=.43$, $p<.001$).

As might be expected on the basis of clinical experience, number of side effects per visit correlated significantly and positively with number of depressive symptoms per visit ($r=.20$, $p<.05$). No other significant relationships were found.

DISCUSSION

These results suggest the following conclusions: 1) patients with affective disorders do have interepisode symptoms that can indicate a degree of instability of mood which can lead to relapse; 2) among illness factors, prelithium frequency of episodes is important in determining response to treatment; and 3) duration of treatment with lithium, rather than blood level, is the important determinant of long-term prophylactic response.

It must be emphasized, as with all retrospective evaluations, that a controlled, randomized study should be done to replicate our results. However, we believe that the natural setting of a lithium clinic

provides a realistic basis for findings on interepisode symptoms in patients with specific ratings who take closely regulated lithium doses and are seen monthly.

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Deceased Members of the American Psychiatric Association

The deaths of these members were reported to APA between Oct. 8 and Dec. 10, 1986.

Anthony M. Abruzzo
John Maxey Anderson
Mallie Lee Barclay
Norton H. Bare
Joseph Bess
Barbara Leigh Boyd
Alex L. Brown
Werdna Foster Cochran
Frederick P. Doyle
Maria Angeles Espanol
Bernard E. Flaherty
Irene L. Hitchman
Christopher R. Hopps
Richard S. Iverson
William A. King
Ernst Kopmann
Irville H. MacKinnon
Lidia Maria Martos
James P. McNeill
Joseph A. Mendelson
Murray C. Miller, Jr.
Don P. Morris
Faith N. Ogden
Felix Peebles, Jr.
Francis X. Pritchard
Edwin R. Ranzenhofer
Reginald S. Rood
Charles I. Schwartz
Charles L. Smith
Jose M. Valverde
David Ray Wood
Richard V. Yazmajian

Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

NEUROSCIENCE

Principles of Neural Science, 2nd ed., *edited by Eric R. Kandel, M.D., and James H. Schwartz, M.D., Ph.D. New York, Elsevier Science Publishing Co., 1985, 926 pp., $47.50.*

This is a monumental text comprising 62 chapters with appendixes covering the field of neuroscience. Neuroscience as a discipline has been exploding with new information, making a revision of the first edition of this book essential. The book is organized into 11 parts addressing basic neuroanatomy and neurophysiology as well as excellent chapters covering the integration of these disciplines with clinical fields such as neurology, psychiatry, and psychology.

This book was used at the University of Iowa to teach a course on neuroscience to medical and graduate students. Because of the superb introductory material, students were able to learn fundamental principles not covered in lectures. The book also served as a reference for topics covered more thoroughly by lecturers. Instructors of the course found the book worthwhile reading; it discussed their particular areas of specialization well and showed where each fit into the discipline as a whole. The fact that the text was applauded by both students having no background in neuroscience and established investigators gives an indication of the quality of the work.

The neural mechanisms of behavior are strongly emphasized, and many studies from experimental psychology are incorporated. It is that aspect which should initially appeal most to psychiatrists. However, the chapters on the molecular biology of the CNS should also be read because they are concise overviews of material that many psychiatrists may not be familiar with, because much of the material is based on research undertaken since most of us attended college. The book illuminates the importance of understanding molecular biology as a key to understanding behavior, something the editors are particularly noted for. Behavior is the manifestation of neural organization; neurons must be understood as cells before our understanding of behavior can be complete.

The book will be an essential text for every medical student. For those of us beyond that level of training, we will have to choose parts of this book and read them to keep up with current events and understanding of neuroscience as it affects clinical medicine. For psychiatrists, most of the book is relevant to our practice, including chapters on behavior, learning, and memory and specific chapters on psychiatric and neurological syndromes. Each chapter is fairly brief and includes splendid diagrams and tables, making each easy to read in one sitting. The chapters on schizophrenia and affective illnesses are rather basic for specialists in the field (the book is not intended to be a text of psychiatry). These chapters do show, however, where these diseases fit into the overall landscape of the CNS. For the reader with no knowledge of psychiatry they are nice introductions that stimulate further reading. They are soundly based on neurobiology and the scientific method, and they discuss issues from a standpoint of research and data rather than stating theories as dogma. Psychiatrists will find the text useful for its neuroscience, not its psychiatry. The chapters are important for introducing nonpsychiatrists to the fascinating world of psychiatry approached as a science from a neurobiological view. The inclusion of these chapters also shows that psychiatry is a part of mainstream medicine, allied with neurology and experimental psychology.

So much clinical information from the fields of psychiatry and neurology is interspersed throughout the entire text that the historical chasm between the basic and clinical sciences becomes diminished. If the field of psychiatry is to continue making significant contributions to man's understanding of the genesis of behavior, an integration of the neurosciences with the clinical pursuits of psychiatry must be emphasized.

The unfamiliar portions of this book are intertwined so gracefully with the familiar that learning is almost effortless and occurs in a logical, progressive fashion. Psychiatrists would benefit from this book's understanding and organization of the great variety of research encompassed in the field of neuroscience, since a great deal of this research will directly influence our understanding of behavior and the neuropathological substrates of mental illness.

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The Integration of Neuroscience and Psychiatry, *edited by Harold Alan Pincus, M.D., and Herbert Pardes, M.D. Washington, D.C., American Psychiatric Press, 1985, 94 pp., $12.00 (paper).*

This overview of neuroscience in psychiatry is part of the Clinical Insights monograph series published by the American Psychiatric Press. As are all monographs in this series, it is brief, easy to read, and instructional. It is not meant to be an exhaustive detailed text, but rather, it serves to provide the practicing psychiatrist with a broad overview. The editors, Harold Pincus of George Washington University and Herbert Pardes of Columbia University, are able to convey excitement and optimism while offering practitioners an organized introduction to new technologies and findings that will directly affect their field. They have chosen contributing authors who are able to impart complicated information in a format that is understandable and enjoyable.

The first chapter, authored by the editors, points out the recent interest in neuroscience by the lay press and national television, suggesting that exploration of the biology of thoughts and emotions is the most exciting "ongoing drama" in medicine. The authors understand that this new approach and its technology might be threatening to psychiatrists currently practicing psychodynamically oriented therapy. They suggest, however, that "psychiatrists who are sufficiently flexible to update their knowledge base continually

and modify their practice accordingly will find the clinical acumen gained through years of working with psychiatric patients will be even more valuable when it is integrated with the information emerging from the neurosciences." They go on to define "neuroscience" and discuss trends in the field.

In chapter two, Robert Post provides a short description of the new computerized brain imaging techniques, including nuclear magnetic resonance (NMR), positron emission tomography (PET), and regional cerebral blood flow. He touches briefly on each technique and then presents findings regarding new pharmacological treatments that have practical implications for physicians currently in practice.

Using the putative role of the neurotransmitter dopamine in schizophrenia as a descriptive example, Steven Paul provides a chapter discussing the current integration of neuroscience into clinical psychiatry. This is followed by a description by Nancy Wexler et al. of the role that molecular genetic techniques play in the understanding of Huntington's disease. This is the most detailed chapter in the book and provides a brief but lucid account of gene linkage and restriction fragment length polymorphism (RFLP) markers. It is apparent that these powerful techniques may yield valuable information in a variety of psychiatric disorders and will become increasingly important to future psychiatric research. The monograph ends with a chapter by Pincus and David Rubinow devoted to descriptive models of interaction between psychiatric and medical disorders and a discussion of their importance to consultation-liaison psychiatry.

Although there is some repetition regarding brain imaging techniques in different chapters, this monograph is successful in its mission. It is concise yet offers an interesting and remarkably current review of the field while containing adequate reference lists for readers wishing to pursue specific topics in depth. There is an overriding optimistic tenor throughout the monograph, and it provides valuable information to the practicing psychiatrist.

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GABA and Mood Disorders: Experimental and Clinical Research, *edited by G. Bartholini, K.G. Lloyd, and P.L. Morselli. New York, Raven Press, 1985, 240 pp., $29.50.*

This text is the fourth in the monograph series from the Laboratories d'Etudes et de Recherches Synthélabo (LERS). Each of the editors contributes significantly to different chapters. The papers here are the results of a symposium on γ-aminobutyric acid (GABA) held in Paris in August 1984.

With the discovery of each new neurotransmitter and neuromodulator the search begins for its relevance to psychiatric and behavioral conditions. First the description of a role for catecholamines in mental illness was presented, but it was soon apparent that many behaviors were under the control of other systems in the brain. The discovery of amino acid transmitters, primarily GABA and glutamate in the brain, has led to a search for their roles in mental illness. The same process is occurring with acetylcholine, the neuropeptides, and other chemicals in the brain such as adenosine. To the credit of current investigators, fewer claims regarding a certain chemical's control of a given brain function (i.e., a behavior) are made. There is still a tendency, however, to make sweeping claims about the responsibility of a given substance for a given behavior. The authors in this book, by the nature of their subject (GABA and mood disorders), tend to do this, although some mention is made about other interacting systems. Our vast ignorance of brain function is acknowledged; any researcher is ready to admit that there are untold numbers of transmitters functioning in as yet unknown ways.

Lest I sound overly pessimistic, I should add that much is known about neurotransmission and its role in behavior. This book gives a succinct account of the role of GABA in the expression and possible production of neuropsychiatric conditions. Impressive data from clinical trials with progabide in treating depression are presented. If these results continue to be replicated, this GABA-mimetic will doubtless be of great benefit to many patients. Encouraging results of trials using this drug in the treatment of tardive dyskinesia are also discussed. Many GABA-mimetics have side effects that limit their usefulness, but this drug seems to be devoid of any. Aspects of the drug's actions are hard to explain with our current understanding of the GABA-benzodiazepine-picrotoxin chloride ionophore, the most obvious being the lack of anxiolytic action of this potent direct GABA agonist. Enough behavioral pharmacological studies are presented to provide background for the clinical section of the book and to demonstrate the effectiveness of progabide in animal models.

This book is an excellent reference for anyone interested in the frontiers of neuroscience in psychiatry. The investigation of the GABA system in behavior has been limited by the lack of nontoxic potent direct agonists. This book details the use of new GABA agonists in defining the function of this amino acid neurotransmitter in behavior. The future for this class of drugs looks bright. However, the notion of one chemical in the brain being responsible for a given behavior is outdated and must be abandoned. This text focuses on one particular transmitter that is undoubtedly part of a host of chemicals and systems working in concert to produce behavior. However, the transmitter under scrutiny is very important, being the most common neurotransmitter in the brain. For technological and other reasons, the catecholamines have assumed a prominent place in psychiatric research. It is time for the limelight to be shared by other, equally important clinical messengers, of which GABA is one.

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Clinical Neuroscience: From Neuroanatomy to Psychodynamics, *by Jay E. Harris, M.D. New York, Human Sciences Press, 1986, 292 pp., $34.95.*

This far-reaching book proposes an "integrated" model of mind-brain function and discusses topics ranging from restructuring *DSM-III* to explanations for major mental illness and the foundation for life stages. For people who struggle with relatively small research problems, the scope of this undertaking may seem impressive if not overly ambitious.

Although Dr. Harris's hypotheses are speculative to a great extent, one of the major aims of this book is to propose a basis for reunifying our field of psychiatry. How can there be any divisions in psychiatry if schizophrenia can be explained by statements such as, "The outpouring of dopamine continues to compel action. Because there is no hope of consummation, the onset schizophrenic experiences subjective deregulation that is attended first by sleeplessness and finally by a full depletion of serotonin resources" (p. 120)? In fact, this book jumps the mind-brain chasm so many times it

begins to make your head spin. Although one might applaud the attempt to heal the divisions within psychiatry and to facilitate the appreciation of strengths in different approaches to the same clinical problem, an attempt to propose a unified theory of mind-brain function seems to be an effort well beyond the current state of our knowledge. As McHugh and Slavney have pointed out in *The Perspectives of Psychiatry* (1), we cannot at this point fully integrate dynamic theories of the mind (i.e., the life story method) with biological findings associated with psychopathology (the disease method) because each perspective gives only partial illumination of the problem and provides a different kind of insight. Thus, we can appreciate several different methods and perspectives in psychiatry because each of them may lead to partial but distinct insights into the same clinical problem.

The substance of the text has strengths and weaknesses ranging from some very innovative ideas of mind-brain interaction and its organizing principles to extremely difficult sentences that will stop fast-reading, slow-thinking readers in their tracks. For example, "It [norepinephrine] constitutes a reality-drive responsible for the impetus to assess and direct perceptual processing of the indications of salience in reality." The last paragraph of the foreword probably states this book's weakness concisely: "The uninitiated frequently find it [the root metaphor] too confusing/abstract/counterintuitive to stick with for very long." On the other hand, this book focuses the reader on the clinically relevant aspects of many of the new discoveries in neuroscience and puts them into an interesting clinical psychodynamic framework.

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HISTORICAL TOPICS

Science and Values: The Aims of Science and Their Role in Scientific Debate, *by Larry Laudan. Berkeley, University of California Press, 1984, 144 pp., $14.95.*

Psychiatry has recently undergone a Kuhnian revolution. Larry Laudan is a Kuhnian revisionist, and in this book he tries to solve some problems left unanswered by Kuhn's philosophy of science, particularly "incommensurability" and "underdetermination." To make any sense of this, it helps to go back a couple of thousand years.

In primitive religious philosophy, mental as well as physical disorders were ultimately attributable to psychic etiologies, which left the victim susceptible to various supernatural forces whose existence could not be questioned and whose tenets could never be proven false (nonfalsifiability) and therefore could also never be proven true. Aristotle and his followers were the first to establish a scientific exception to philosophy based on myths and superstitions, and Hippocrates applied similar thinking to medicine. The Greeks proposed theories based on observation but did not establish a more specific scientific method for solving disputes over theory. Then their influence was overwhelmed for about 2,000 years by a resurgence of religious philosophy based on nonfalsifiable revealed truth. Scientific philosophy began to progress again with Bacon and Newton and the development of the scientific method. Newton's philosophy of science did not permit hypotheses (*hypotheses non fingo*) and excluded unobservable entities, since inductive methods could be applied only to observable bodies (p. 81). By the late nineteenth century most scientists had given up on the Cartesian aim of establishing infallible knowledge, settling instead for the highly probable knowledge reflected in today's ubiquitous p values (e.g., $p \leq .05$). They gradually came to allow, even to expect, hypotheses. Psychiatrists like Kraepelin were following the example of those working successfully on infectious diseases, using enumerative and eliminative induction to establish discrete disease entities, after which specific etiologies might be sought: nosology preceded etiology.

While most of science continued in a realist vein, progressing without much interruption to the "rational positivism" currently represented by Karl Popper, psychiatric philosophy experienced a Kuhnian revolution as Sigmund Freud's ideas came to dominate. Kuhn (1, 2) divided science into normal (that which doesn't affect the dominant way of thinking) and abnormal (that which shakes the foundations of the ruling group's ideas). He argued that revolutionary theories come in sets, accompanied by new methods for solving disputes about theories and new values for solving disputes about methods. The new values also decide which questions deserve to be explained and which facts deserve to be considered. He called such a change a "paradigm shift." Since there is never adequate evidence objectively to pick one set of theories, methods, and values over another (underdetermination), the reason for choosing one paradigm over the other can be reduced to a matter of taste. The new and old schools have difficulty communicating with each other because they resolve disputes about facts by different methods. In fact, they can't agree on what constitute the relevant facts to be explained or which are the "permissible problems" worthy of solution. Kuhn calls this "incommensurability."

While the "realists" had taken descriptive nosology as the primary problem requiring dissolution and then discovered the etiologies of general paresis and pellagra, the Freudians maintained little interest in nosology but concentrated on etiology, which they held to be unobservable. Some of their theories, such as reaction formation and displacement, rendered their paradigm logically unfalsifiable and therefore unverifiable. Their debates over theory were usually settled when one participant established the dominant position of psychotherapist to the other. Psychiatrists who insisted on maintaining the scientific method had to become neurologists or work in the unfashionable asylums where patients with observable pathology were kept. But psychoanalysts became advisors to the rich and powerful, who could afford to pay doctors to listen to them. Although the "realist" philosophers never accepted psychodynamics as science, Kuhn's philosophy allows it to be so considered. Laudan cites its emergence as an example of a Kuhnian scientific revolution, with change on all three levels.

Psychiatry has again come to be dominated by those who value falsifiable hypotheses. Interested in nosology and encouraged by the discovery of antipsychotic and antidepressant medication, lithium, and NIMH grants, these newcomers rode to tenure, then to power on the now demonstrably falsifiable catecholamine and minimal brain dysfunction hypotheses. The *ancien régime* could correctly point out that these counterrevolutionaries have not discovered "infallible knowledge," that many of their p values cancel each other out, and that their reasons for choosing this updated old

paradigm involve a personal and subjective Kuhnian "leap of faith" deeply rooted in their collective unconscious psychopathologies. But no one is listening.

In *Science and Values,* Laudan argues for a more gradualist, "historically faithful" picture of scientific change. He lists many exceptions to Kuhn's revolutionary contributions. Most of his discussions begin with Kuhn's premises, but in the final chapter he also offers "a reticulational critique of realist axiology and methodology."

The book is clearly directed to philosophers. To make any sense of it, a psychiatrist would need previous knowledge of both Thomas Kuhn and of academic philosophy's "baf-flegab," which is quite different from ours. The basic problem is that, although gradual changes (what Kuhn would call "normal science") can eventually result in fundamental changes in psychiatry, our revolutions are more interesting. Laudan's exceptions to Kuhn are like a visible pattern of mosquito bites on an unseen giant's skin. The principal effect this book will have on psychiatrists will be to make them want to read Kuhn.

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Psychotherapy in the Third Reich: The Göring Institute, *by Geoffrey Cocks. New York, Oxford University Press, 1985, 318 pp., $24.95.*

This book offers an unusual glimpse into the workings of bureaucratic psychotherapy during the Third Reich. As one might anticipate, the Nazis were ruthless toward certain psychotherapists, as is illustrated by their ostracism of Jewish therapists and their beheading of the left-leaning psychotherapist John Rittmeister. The author, however, contends that all was not bleak for psychotherapy in the Third Reich and that the Nazis not only tolerated but promoted psychotherapy when it was set in the context of Nazi ideals.

The primary institutional locus of psychotherapy in Nazi Germany was the Göring Institute, an organization dedicated to the protection and promotion of psychotherapy within the Nazi regime. The Göring Institute was formed in 1936 by the merger of two very different organizations: the German General Medical Society for Psychotherapy, a group of German psychotherapists who wanted to foster the psychotherapeutic enterprise within Nazi Germany, and the Berlin Psychoanalytic Institute, which had been recently purged of its Jewish membership. Headed by Matthias Heinrich Göring, cousin of Nazi minister Hermann Göring, the Institute allowed a wide range of psychotherapeutic views. Both lay and physician therapists were admitted to the Institute, and even psychoanalysis was tolerated, as long as Freud was not aggrandized and Jews were not significantly involved either as therapists or patients.

Cocks attributes the acceptance of psychotherapy in Nazi Germany to several factors. Not only did M.H. Göring, the leader of the Göring Institute, have impeccable Nazi credentials, but many therapists within the Göring Institute were able to argue successfully that the goals of psychotherapy were compatible with certain Nazi concerns, particularly the Nazi ideals of preserving and purifying racial character and will. Further, psychotherapy was a departure from the therapeutic nihilism of contemporary German psychiatry. Although psychotherapy was not considered appropriate for hereditary degenerates and racial outcasts, it could offer the possibility of rehabilitation to individuals of desirable racial stock who might otherwise be condemned to institutionalization or even extermination because of their mental disorders. Cocks describes the supporters, dissenters, and professional "survivors" involved in psychotherapy in Nazi Germany during the 1930s and early 1940s. He concludes by suggesting that despite the unsavory aspects of the Third Reich, "the nature of Nazi governance produced, on the institutional level, more opportunity than oppression for the evolving profession of psychotherapy" (p. 249). Cocks argues that following the war, psychotherapists were in a much stronger position to challenge establishment psychiatry in Germany because of the development of psychotherapy as a profession under the Third Reich.

Perhaps Cocks's greatest contribution is reminding us that Nazi Germany was not entirely devoid of intellectual activity and that one can learn something about psychiatry in the twentieth century by trying to understand the development of psychotherapy under Hitler's rule. But herein lies the weakness of this book as well, for instead of addressing the crucial question of how cultural forces shape the theoretical aspects of psychotherapy, Cocks focuses most of his analysis on how the Göring Institute enabled psychotherapists to defend their turf against biologically oriented psychiatrists—a question of relevance in the 1980s but certainly of less importance for understanding events in Germany during the 1930s and 1940s. For instance, Cocks devotes part of a chapter to the Institute and the S.S. and raises a host of questions about the Institute's approach to homosexuality, infertility, and the treatment of members of the Nazi elite. But the problem of how the very evident alterations in ideology and therapy of the Institute therapists shed light on the process by which culture and psychotherapy are related generally goes unexplored.

Nonetheless, Cocks has written an extensively documented and thought-provoking account of one aspect of psychiatry under Hitler. Although readers expecting an analysis of the relationship of Nazi culture to the practice of psychotherapy will be left wanting more, the book takes its place along with Alan Beyerchen's *Scientists Under Hitler* (1) as a significant contribution to our understanding of the nature of scientific activity in the Third Reich.

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The Social Transformation of American Medicine: The Rise of a Sovereign Profession and the Making of a Vast Industry, *by Paul Starr. New York, Basic Books, 1982, 495 pp., $24.95; $11.95 (paper).*

How does one review a book that won the 1984 Pulitzer Prize for general nonfiction, the 1984 Bancroft Prize in

American history, and the 1983 C. Wright Mills Award in sociology? Very carefully. My initial reaction to Paul Starr's *The Social Transformation of American Medicine* was that it is positive, upbeat, and very informative. I thought that this book was must reading for all students of the history of American medicine, a detailed but clear presentation of the rise of organized medicine in the United States. And yet it left a bad taste in my mouth. Professor Starr reduces "the rise of a sovereign profession and the making of a vast industry" to one force, the profession's pursuit of wealth and power. Am I being defensive, I thought, isn't this the commonly held belief? Is the major force behind medicine's rise to supremacy in health care delivery the acquisition and retention of power and wealth? I certainly hope not.

In *Professor of Medicine* (1), Eliot Freidson stated that he believes the preeminence of physicians in the health care field is based on their knowledge. The autonomy that physicians perceive having is in fact a state of controlled right. That is, the medical profession receives its power by licensure and statute; it has a state-controlled power. The physician does, however, control the division of labor in medical practice. When practice was office based, the physician was to a much larger degree autonomous. But as technology advanced, much of health care delivery and certainly the more expensive aspects of health care shifted to hospital settings, where the physician is confronted with a division of labor organized and administered independently of the physician's private practice. Control in many hospitals has increasingly passed to the boards of directors and administrators of those hospitals. Although he wrote in 1970, Freidson may have identified early the beginning of the decline of the sovereignty of medical practice and the making of a vast industry owing to the breakdown of the physician's ability to control the divisions of labor.

In her review of Professor Starr's book (2), Florence A. Ruderman, an associate professor of sociology at Brooklyn College, wrote that Professor Starr's theoretical perspectives are neither new nor illuminating. Professor Starr denies that medicine's authority grew because the science of medicine and, with it, the "verifiable" knowledge of the clinical practice of medicine grew. Starr contends that, beginning in the mid-nineteenth century, Americans grew dependent on medicine as they "lost their self-assurance, became increasingly dependent on outsiders, because of a loss of faith in the common man, and in common sense; a loss of pre-industrial skills that made for self-sufficiency; increasing urbanization and industrialization; rising societal tensions and instabilities; the conflicts created by capitalism; the isolation of the nuclear family; the progressives' search for a new order; and science, which convinced men that the world was complex—not simple, as they had previously thought." Partly true, partly false, partly nonsense.

The theoretical views put forth by Professor Starr are limited, presented by an "outsider" who minimizes the impact of science and technology in medicine's growth and rarely discusses the moral, cultural, political, and intellectual currents that flow through society as a whole and the impact they have had on this growth.

Book one (the book is laid out as two"books"), entitled A Sovereign Profession, details the early days of American medicine and is fascinating reading. From colonial America to the emergence of capitalism in American medicine in the 1930s, the book describes the acquisition of medical knowledge and respectability, hospital growth, and the conflict between public health and private practice.

Book two, The Struggle for Medical Care, details organized medicine's downfall: the lack of social reform, rise of Social Security, development of private health insurance, the influence of unions and organized labor, exploding health care costs, "losing legitimacy," and the growth of corporate medicine.

I still believe that *The Social Transformation of American Medicine* is a worthwhile, informative, stimulating work, but, like many books that try to be comprehensive, it is stilted. It presents as fact what at times is opinion, and the theoretical hypotheses it sets forth are simplistic. It should be read by all who ask, "How did we get into this mess?" what with HMOs, PPOs, IPAs, PROs, Medicare freezes, and threatened autonomy. It needs to be balanced, however.

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NEUROLOGY

Textbook of Child Neurology, 3rd ed., *by John H. Menkes. Philadelphia, Lea & Febiger, 1985, 827 pp., $58.50.*

Deservedly, this text has been something of a standard ever since the first edition in 1974. Dr. Menkes has substantially expanded and updated his work while keeping it consistent with the intent of the earlier editions to incorporate the most recent knowledge of pathophysiology into clinical evaluation and management. Accordingly, the book is divided by broad classes of etiology, with chapter headings such as "Metabolic Diseases of the Nervous System," "Infections of the Nervous System," "Chromosomal Anomalies," and so on. This approach may be contrasted with organization according to prominent symptoms found in other texts, such as *Paediatric Neurology* (1), that include chapters such as "Ataxia" or "Localized Weakness." Both approaches have strengths and are, to some extent, complementary. The former approach may be the less useful for a beginning student.

Unlike many other child neurology texts, no edition of this one has ever included any "how to" chapters on such things as the pediatric neurological examination or electrophysiology. The preface to the first edition referred anyone in need of help in such areas to other texts. The third edition continues to avoid methodologic sections despite acknowledging the advancing technology. Although superficially it might appear that Dr. Menkes has chosen to ignore the student, this is belied by the attention given to clarity of explanation. To produce a text of reasonable size and affordability (certainly a student imperative), choices had to be made. Reminiscent of Merritt's textbook of general neurology (2), in this volume Dr. Menkes and the other contributors have chosen to focus on making each chapter as rich as possible with detailed descriptions of disease pathologies, clinical presentations, differential diagnoses, and treatments, all of which are extensively referenced.

Although the list of additional contributors has been increased from four to six, to a very great extent this is still

a one-author work. Ten of the 15 chapters were written by Dr. Menkes alone. Theoretically, this fact could make for a more parochial outlook. However, this nonneurologist, at least, is hard pressed to find evidence of this. One is reassured, also, by Dr. Menkes's clear indications that certain issues, such as whether hepatic needle biopsy and assay of phenylalanine hydroxylase should be part of the initial diagnostic workup of hyperphenylalaninemia, are not resolved and that the opinion given is his. The advantages of a predominantly single-author approach are evident in the consistency of organization and style and in the lack of redundancy between chapters.

Those who are familiar with the earlier editions will find the same lucid prose and the same straightforward plan of organization. The fact that nearly all the chapters have the same titles as in previous editions gives a deceptive impression that little has been changed. In fact, close comparison of equivalent chapters in the second and third editions reveals not only updating and addition but also rewriting of previous material to add clarity and conciseness. Consistent with the emphasis on packing a great deal of information into a limited space, tables, illustrations, and photographs are frequently and effectively used, perhaps more liberally than in previous editions. These seem to be directed at all levels of experience. The student, for example, will find a useful diagram of how to recognize the fingerprints of children with Down's syndrome and a sequence of pictures depicting chorea. The experienced physician may find a positron computed tomographic scan used to localize an epileptic focus of more interest.

Two new chapters have been added to this edition: "Cerebrovascular Disorders" and "Neurological Manifestations of Systemic Disease." The former chapter, which limits itself to congenital abnormalities of the cerebral arteries and veins and ischemic and hemorrhagic lesions resulting from disease processes affecting the cerebral vasculature not covered in other chapters, is added without specific explanation. Although the general topics covered in this chapter appeared in various parts of other chapters in the previous edition, they are covered more thoroughly and coherently here by bringing them together in one place. The other new chapter, the preface explains, was made necessary by the emergence of new disease entities resulting from the increasing numbers of children surviving end-stage renal disease and various malignancies. Certain disease entities covered here, such as pellagra, are new only in context. Others, such as dialysis dementia, are truly new and are currently the subject of intense study. This chapter is, thus, invaluable and may well alone justify the expense of replacing a previous edition of this text.

For child psychiatrists, the final chapter, "Disorders of Mental Development," will be most directly relevant. This chapter, written by Marcel Kinsbourne, deals with mental retardation, infantile autism, disorders of speech and language, specific learning disabilities, school failure, and hyperactivity. Inevitably, these topics must be covered in a fairly brief manner, but the author manages both to touch on the important features of each problem and to present these disorders from a clearly neurological perspective. Some of the references are quite timely. For example, the fact that many autistic children have elevated blood serotonin levels, which has been known for some time, is supplemented by mention of the recent work of Todd and Ciaranello relating elevated blood serotonin levels in some autistic children to elevated titers of antibody to a serotonin receptor binding protein.

The third edition of *Textbook of Child Neurology* should prove an ideal reference work for physicians, psychologists, and some educators who work with children. As a consequence of being organized by disease and of not including more general sections illustrating how to integrate the history, physical, and laboratory findings into a diagnosis, this work is somewhat less accessible than other pediatric neurology texts to students early in their medical career. However, it is an excellent aid to thought for a clinician at any level. This is the book to pick up when you have arrived at a preliminary differential diagnosis. Information is presented with enough clarity for the student and enough detail and referencing for the experienced physician. The student who expects to have more than a temporary need for a pediatric neurology book will find that this text retains its usefulness for years as he or she becomes increasingly experienced, whereas less focused texts may seem to become too general. For those who already have a previous edition of Dr. Menkes's work, the always difficult question of whether to update may be decided by the excellent new chapter on neurological manifestations of systemic disease.

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Vascular Aphasia, *by Joseph M. Tonkonogy. Cambridge, Mass., MIT Press, 1986, 220 pp., $30.00.*

When compared with many volumes on the clinical aspects of aphasia that have appeared in the past decade, *Vascular Aphasia* presents a number of unique characteristics. It is written by a Russian neurologist who was Chairman of the Department of Neurology at the Bechterev Psychoneurological Institute in Leningrad. The author studied and made use of A.R. Luria's neurolinguistic approach to aphasia in his clinical practice. Dr. Tonkonogy now serves as Chief of Neurology at the Northampton Veterans Administration (VA) Medical Center in Northampton, Mass., after having spent several years working in the Aphasia Research Center of the Boston VA Medical Center. He writes authoritatively, having gained experience in two separate approaches to aphasia, and offers his own synthesis of this background.

Dr. Tonkonogy emphasizes the dynamic changes that occur in language disturbance during the recovery stages that follow a cerebral vascular accident. He stresses the fact that the single, static picture presented in most books is inadequate to describe aphasia. Many of the case histories in this volume delineate language disturbance through the acute, subacute, and chronic phases of recovery from stroke. For the many clinicians who primarily evaluate patients during the early, acute states of aphasia and find most of the literature difficult to apply, the insights presented in this volume may be of considerable value.

The author opens with a discussion of the classifications of aphasia, always a difficult task. He contrasts the early localizationist and holistic approaches and ends with a more modern "neurolinguistic" classification. Even though it re-

flects the concepts of Luria, the neurolinguistic approach appears suspiciously close to the classic localization classification. Dr. Tonkonogy next discusses the individual symptoms of aphasia, including motor expression, comprehension, repetition, reading, writing, and calculation, and presents a fairly detailed rating scale of the major symptoms for use in the study of the aphasic patient. The latter provides an excellent guide for grading severity of various aspects of aphasia.

The second major section of the book deals with the syndromes of aphasia as seen in stroke evolution. The major division is into anterior and posterior aphasias, with a third, mixed category (anterior-posterior) and a final subcortical division. Case histories, in many instances illuminated by postmortem descriptions, are used to illustrate points throughout this discussion. Finally, the author discusses localization of aphasia symptoms and correlates these symptoms with vascular pathology.

The book has several notable values. First, it contains a large number of well-studied cases, evaluated by a single person in a consistent manner and presenting both clinical and pathological data. Second, it presents the syndrome approach of Luria, a classification known but rarely practiced in the United States. Third, the author recognizes and discusses the dynamic quality of aphasia, a point too often overlooked in presentations of aphasia.

The book does have several faults. There is a dated quality, notable primarily through the absence of data linking modern imaging tests such as computerized tomography or magnetic resonance scanning with the aphasia syndromes. The number of postmortem correlations presented, more than I have found in almost any other study, partially compensates for this lack. Nonetheless, the contemporary clinician will note the absence of the major innovations in neurological diagnosis of the past decade. In addition, the author's detailed and ongoing case histories are sometimes difficult to read. Although they provide excellent examples to support points made by the author, the number of clinical details available tends to detract from the strength of the presentation.

Vascular Aphasia is certainly a useful volume, particularly for its demonstration of a relatively current Russian approach to the aphasias. It is apparent that this approach resembles much more than it differs from the classic European-American approach. The clinical material presented is excellent, and the theories of language function presented by the author are restricted and, in most instances, supported by good examples. The volume will be of considerable interest to students of language disorders.

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FOR A GENERAL AUDIENCE

How You Can Help: A Guide for Families of Psychiatric Hospital Patients, *by Herbert S. Korpell, M.D. Washington, D.C., American Psychiatric Press, 1984, 142 pp., $15.95; $9.95 (paper).*

During the last few years, psychiatrists have been showing increasing interest in the families of their patients. The activities of such advocacy groups as the National Alliance for the Mentally Ill, the reawakening of concern about "family burden," and findings from studies of supportive family therapy are bringing the family of the psychiatric patient into prominence.

This volume, which is addressed specifically to families of psychiatric hospital patients, is a valuable contribution to the growing literature for families of the mentally ill. Dr. Korpell discusses families' reactions to mental illness, reasons for psychiatric hospitalization, and the bewilderment and frustration families often feel when a member requires hospitalization. He describes how the typical psychiatric hospital functions and how a patient is evaluated. The chapter devoted to psychiatric diagnosis explains *DSM-III* criteria in simple terms. The chapters on treatment in psychiatric hospitals and psychiatric medications will be especially valuable to families. In addition, the author describes the actions and side effects of commonly used medications. Some excellent suggestions for further reading are listed.

Dr. Korpell's small book attains its objectives. It is written simply and clearly and from a commonsense, eclectic point of view. Constructively and nondogmatically, it supplies families with the information they need.

I shall recommend this book to my patients' families, particularly families of those who are being hospitalized. Families of psychiatric outpatients, too, will find that this excellent, concise work is helpful. I predict that it will be both widely read and valued by troubled families who, too often, have been overlooked rather than given information enabling them to form a therapeutic alliance with psychiatrists for the benefit of patients and all others concerned.

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Straight Talk, No-Nonsense Guide to Better Sleep, *by Lynne Lamberg; edited by the American Medical Association. New York, Random House, 1984, 342 pp., $8.95 (paper).*

Physicians and psychiatrists have long had an interest in sleep and its disorders. Hippocrates and other famous physicians of ancient times knew about insomnia as a key symptom of depression and speculated about the curative benefits of "restful sleep." In our own century, Freud's "The Interpretation of Dreams" (1) stimulated great interest about dreams among both mental health professionals and the public and led to more general questions about sleep. Aserinsky and Kleitman's discovery of rapid eye movement (REM) sleep in 1953 opened up a new era of sleep research, leading initially to many discoveries about the phenomenology and physiology of sleep in both normal subjects and patients. Psychiatrists have played an important role in these developments—for example, with EEG sleep laboratory studies of sleep disturbance in depression.

During the past 15 years or so, particular attention has been given to sleep disorders medicine. More than 200 clinical centers have been established around the country for evaluation and diagnosis of patients with complaints related to sleep and wakefulness. A new medical subspecialty appears to be emerging to care for these patients. This specialty comprises psychiatrists, psychologists, pulmonary specialists, neurologists, ear-nose-and-throat surgeons, and other specialists from many fields.

A nosology of sleep disorders is also emerging from the experience of seeing thousands of patients. Four major types of sleep disorders have been delineated: 1) the disorders of initiating and maintaining sleep, or the insomnias, 2) the disorders of excessive daytime sleepiness, 3) disorders involv-

ing the circadian sleep-wake cycle, and 4) disorders involving abnormal behaviors during sleep, such as sleep walking, enuresis, and nocturnal epilepsy.

Part of the AMA's Home Health Library, *Guide to Better Sleep* was written by Lynne Lamberg with the medical advice of William C. Dement, M.D., Ph.D., Shervert H. Frazier, M.D., and the late Elliot D. Weitzman, M.D. It provides an up-to-date review of current knowledge of normal sleep and sleep disorders. Intended for the general public, this book is also a good introduction to modern sleep research and sleep disorders medicine for the clinician. It is nontechnical and well written, with many interesting anecdotes. It also provides many practical suggestions about both the self-management of sleep problems and when to seek professional help. It is the best book available for the clinician to recommend to patients who want to learn more about sleep and their own sleep problems.

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After Middle Age: A Physician's Guide to Growing Old and Staying Healthy, *by Richard Jed Wyatt. New York, McGraw-Hill Book Co., 1985, 347 pp., $19.95.*

This is a vade mecum for the elderly; it covers the entire spectrum of aging from the basic philosophy of aging to such matters as living independently; nutrition and diet; foreign travel; psychological and psychiatric problems; the aging mind; the nervous system; seeing, hearing, and smelling; alterations in the skin, nails, and hair; disorders of the bones, muscles, and tendons; colds, flu, and more serious problems of the lungs and respiratory system; disorders of the heart and circulatory system; disorders of the digestive system; disorders of the urinary system; disorders of sex, genitals, and endocrine glands; cancer; what to do in emergencies; hospitals, nursing homes, and outside care; paying for physicians, hospitals, and nursing homes; death; and a note to children and grandchildren.

To review this book critically would require a comprehensive knowledge of geriatrics and gerontology that only a Renaissance man like the author could possess. However, on the basis of my personal experience over the last 86 years, I found the exposition in this book most helpful and quite in keeping with my own style of life. I shall keep it by my bedside as a ready reference in times of quandary or emergency.

The author is fully aware of the fact that his book is only a beginning. He states in his preface, "This book was written not only to educate the reader; I hope to learn from the reader, also. I have a commitment to making aging easier and would appreciate hearing from readers who find errors or have advice that might be passed on to others in future editions."

An often made distinction in aging is the differences between normal senescence and deterioration. This book may well become a guide to the path of natural senescence and, one hopes, the avoidance of unnecessary deterioration. The first paragraph of this review listed the topics for the 23 chapters in the book. Each of these chapters contains some of the distilled wisdom of past ages regarding the aging process, and one wonders how the author, young as he is, was able to make such a valuable selection from this vast reservoir. Among the gems that I spotted are the importance of working in warding off the ravages of age; the list of do's and don't's, with an indication of where they appear in the book; sources of available information in print (page 7); a guide for vegetarians (page 30); travel abroad; a chapter on psychiatric and psychological problems, including advice about treatment of anxiety, depression, suicide, insomnia, and alcoholism and a didactic explanation of psychotherapy (chapter four); an especially good chapter on the lungs and respiratory system, including discussions of colds, allergic rhinitis, and sore throats; and a section on what to do in emergencies.

As the author suggests, the aging process does not begin at any particular period of life; it is a continuous process. In fact, aging is probably accelerated more at the beginning of life. Consequently, the book is useful for readers of all ages. It is "written for those who wish to begin now to meet the challenge of aging"(from the preface).

There is one area that the author has not delved into, the "post-retirement age" for those who refuse to retire, a phenomenon that seems to be increasing as the gap between span of life and enforced retirement increases. Recently I was asked to participate in a symposium entitled How Does It Feel to Grow Old? which is to appear in *Integrative Psychiatry*. After indicating to the editor that I could not answer the question because I do not feel old, I added that perhaps I could write on why I don't feel old and that might serve as a guide to those who continue their careers despite passing the conventional Rubicon of retirement age.

I no longer engage in laboratory work directly but still keep an eye on organization, administration, and evaluation of results. The actual work is carried on by a group of youthful zealots, each with his or her own special talents, who are imbued with the desire to find out how the brain relates to the mind and behavior not only on the basic level but also on the applied level—detecting vulnerability to mental disorders and defining the role of psychosocial factors in the development, maintenance, and amelioration, if not cure, of mental disorders. This is the mandate which has long stood on the masthead of our biometric approach to psychopathology.

Regarding ambitions and plans for the future, there seems to be no letup in new ideas and developments. Perhaps the growth and development of plans and ideas stem not so much from me as from the coterie of young colleagues who surround me like the cambium around an old tree. While the interior may be more or less static and dry, the vital cambial cells provide the viability and progress of new undertakings. It is this cambial layer which keeps me alive and in touch with new developments.

In fact, it is the social network provided by this cambial layer that is perhaps the most important change that I have felt. Formerly, although always surrounded by students and younger colleagues in my Columbia days, I never appreciated their full significance and never felt their presence consciously. Now I have grown more dependent on them, and they are one of the reasons why I cannot retire. Their inspiration will make it possible for me to continue and finally die with both my boots and my wits on.

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FORENSIC ISSUES

Aggression and Dangerousness, *edited by David P. Farrington and John Gunn. New York, John Wiley & Sons, 1985, 271 pp., $46.95.*

Dangerousness: Probability and Prediction, Psychiatry and Public Policy, *edited by Christopher D. Webster, Mark H. Ben-Aron, and Stephen J. Hucker. New York, Cambridge University Press, 1985, 225 pp., $32.50.*

These two books have similar titles and were both published in 1985, yet there is surprisingly little overlap between them. Both are edited books: *Aggression and Dangerousness* was edited by David P. Farrington of the University of Cambridge and John Gunn of the University of London; *Dangerousness* was edited by Christopher D. Webster, Mark H. Ben-Aron, and Stephen J. Hucker, all of the University of Toronto.

The first book is the final volume of the series Current Research in Forensic Psychiatry and Psychology and includes an international cast of contributors and a very broad range of subject matter. In fact, with topics ranging from the neurobiology of sexual aggression to the psychodynamics of borderline patients to the management of dangerous patients in Zimbabwe, it is difficult to determine what the focus of this book really is. Nonetheless, most of the chapters have some stimulating material to consider.

After a brief introductory chapter by the editors, Robert Prentky gives a good overview of some very complex neurobiological findings. He relates plasma testosterone to the feeling of anger rather than to its expression in antisocial behavior and states that social learning and cognition are capable of overriding the testosterone effect and determining behavioral outcome. In chapter three, Widom and Newman compare different diagnostic criteria for psychopathy and state that they may all be monitoring some common factor. In chapter four, Gudjonsson and Roberts discuss the phenomenon of lower electrodermal arousal in psychopathic patients than in normal control subjects. These authors report that some hospitalized psychopathic patients have high levels of anxiety and poor social skills and that they might benefit from a therapeutic approach different from that for typical psychopathic patients. Chapter five, by Mullen and Maack, contains a very good discussion of male and female rivalry, envy, and jealousy. Of particular interest is the reported lack of the expected negative correlation between the bizarreness of a delusion of infidelity and the actual occurrence of infidelity. The authors note that the truth or falsehood of a belief may not be the ideal measure of pathology. Further, although pathological jealousy may be a manifestation of a variety of mental disorders, many individuals with paranoid personalities or states may show jealousy in the absence of other symptoms, supporting the validity of these diagnostic entities. The chapter on psychodynamics by Gallwey was difficult to relate to the others in content and methodology; it contains the kind of generalizations that seem out of place in this type of book. The second portion of the book contains a broad spectrum of papers dealing with management of dangerous patients and the need for secure facilities, more longitudinal follow-up data, and awareness of cultural diversity.

The second book, *Dangerousness,* also contains a broad amalgam of issues and approaches that were reworked from lectures given in Toronto during 1981–1982. As in the first book considered, many of the contributions differ considerably from each other but are generally quite good. In the first chapter, Alan Stone reminds us of the need for better research on which to base predictions and cautions that many clinicians may be tempted to predict dangerousness (which they typically do poorly) when they should be focusing on treatment. He also rightly points out that the justice system's problems go far beyond any that could reasonably be blamed on psychiatry. I am not so sure, however, that I agree with his assertion that there are no solid empirical grounds on which to predict dangerousness.

In chapter two, Prof. Greenland points out how sociopolitical judgments color our interpretation of behavior, requiring that situational variables be taken into account before a violent act can be related to a mental disorder. He also does a good job presenting and balancing concerns over false-positive and false-negative predictions. My only major qualm is the summary of factors in criminal violence; what troubles me is that the heterogeneity of violent behavior is not acknowledged. Rather than general predictors, I believe we need to move toward specific predictors for specific types of offenders—for example, predatory criminals differ from psychotic offenders.

Since chapter three is a speculative essay about Dr. Fischer of Geneva, a character in a Graham Greene novel, I will not comment on it in detail here, except to note that it was fun to read, contained useful references to the scientific literature, yet seemed quite out of place in this book.

Chapter four, by R. Brian Haynes, contains some helpful comments on methodological principles and how they can be useful in approaching clinical problems. This kind of presentation is often dry and hard to read, but the author uses examples that elucidate both the points being made and their relevance. In chapter five, Barry Martin illustrates the problems of reliability in psychiatric diagnoses and some useful approaches (such as standardized interviews and tests), but he concludes that getting clinical (and forensic) psychiatrists to use these more reliable methods is another, more difficult problem.

In chapter six, Park Elliott Dietz presents an array of potential predictor variables and emphasizes the importance of finding objective criteria. He also notes that poor prediction should be expected when evaluations are not comprehensive. Learning the details of a person's violent behavior is properly emphasized. Of course, many of the hypothesized predictors would be controversial, but I strongly agree with his conclusion that clinicians should not predict crime without sufficient knowledge about crime.

In chapter seven, Donald Dutton describes an approach to solving the problem of wife assault. Chapter eight, by Menzies, Webster, and Sepejak, makes several important points, including the importance of longitudinal data, feedback as to accuracy of predictions, attention to relevant situational factors, and the need for more methodologically sound research.

In chapter nine, Henry Steadman considers the shifting of patients between the criminal justice system and the mental health system. He reports several interesting pieces of information, such as 1) state hospital admissions have not declined, but the length of stay has, which accounts for the decrease in state hospital populations with deinstitutionalization, 2) more psychiatric inpatients had previous arrests in 1978 than in 1968 (55.6% versus 38.2%), 3) during these years the percentage of inpatients with previous admissions has also increased, 4) the proportion of prisoners with previous state hospital admissions has not increased, and 5) arrests of patients entering the mental health system in

1978 were more likely to be for violent crimes and less likely for nuisance offenses than they were in 1968.

Chapter 10, also contributed by Barry Martin, points out that involuntary commitment rates have remained rather constant while statutes have changed, suggesting a constant rate of severe mental disorder requiring hospitalization and treatment. In chapter 11, there is an extensive discussion by Prof. Bernard Dickens of certain implications of the *Tarasoff* case. This material may be both difficult to read and troubling for mental health professionals, but it is persuasive nonetheless. The final chapter, by Virginia McFarlane, uses a mock trial format to summarize arguments for and against the use of mental health professionals in the prediction of dangerousness.

Overall, both of these books demonstrate a major problem of most edited books: a lack of consistency and focus, with great variations in topic and perspective between chapters. Since *Dangerousness* contains a more homogeneous collection, it seems less "scattered" in focus than *Aggression and Dangerousness*, but that also is a problem in that the former book is repetitive at times. Methodological issues, consequences of false-positive versus false-negative predictions, and discussion of the *Tarasoff* case all appear in several chapters, but arguments could be made for their repetition because they are important issues. Overall, I found both books to have many interesting and worthwhile chapters. Since John Monahan's work (1) is cited repeatedly in both books, it would certainly seem appropriate for the reader who is interested in dangerousness and mental disorders to start with his book before proceeding to those reviewed here.

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Law and the Mental Health System: Civil and Criminal Aspects, *by Ralph Reisner. St. Paul, Minn., West Publishing Co., 1985, 690 pp., $28.95.*

More than a decade ago University of Illinois Law Professor Ralph Reisner began developing teaching materials for use in law school instruction, but when he was invited, in 1976, to teach a course on mental health law in the department of psychology and one for residents in the department of psychiatry, he sought to make his material suitable for all of these settings. This book is the result of that effort, representing years of work. Those familiar with law school teaching materials will find this publication familiar in that it consists of the original text of court opinions plus excerpts from journal or newspaper articles, followed by questions and comments.

The book is divided into two principal parts. The first, The Mental Health Professions and the Law, deals with the structure of the mental health professions (pages 2–48) and the duties owed by practitioners and researchers to patients or clients. These duties are defined as providing reasonable care (pages 49–131), rendering treatment within the boundaries agreed on with the patient or defined by law (pages 132–201), and preserving the confidence of the client (pages 202–269). The second part, The Mental Health Systems, shifts the focus to the issues and rules at the interface between the mentally ill or incapacitated individual and the institutional systems and processes designed to deal with such individuals. This part includes materials on the legal parameters of voluntary (pages 270–310) and involuntary (pages 311–489) psychiatric hospitalization, the special issues involved in the protection of the mentally incompetent (pages 490–534), and finally, the mental health issues which relate to the criminal process (pages 535–690). The book closes with the case of John Hinckley, Jr., the would-be assassin of President Reagan, including excerpts from the transcript of testimony given at the trial. Many readers will find this part of the book amusing but for the tragedy. When one of the experts was asked to explain "schizoid personality disorder," which he had given as Hinckley's diagnosis, he implied that it might be applied to cowboys, computer operators, librarians, forest rangers, and others who avoid interaction with people (page 628). Librarians may find this a sufficient reason not to order the book.

The field of law and psychiatry has undergone rapid, substantial change during the past two decades, and courses or seminars on the subject have become part of the curriculum of the majority of law schools. Formerly, the market was limited, and it remains relatively small compared with traditional areas of the law, so publishers have been hesitant to take on this teaching material. This book is published by West Publishing Company, which holds a virtual monopoly in the legal field. In 1980 it published Prof. Fred Cohen's *The Law of Deprivation of Liberty: A Study in Social Control* (1), which focused on the commitment process and, as the title indicates, on the deprivation of liberty. It fed the "antipsychiatry" atmosphere of the 1970s, and fortunately, one might say, the book was not widely adopted. The leading casebook came to be the more balanced work by Prof. Alexander Brooks, *Law, Psychiatry and the Mental Health System* (2), a 1150-page volume published in 1974 by Little, Brown, and Company, which was supplemented by a 349-page booklet in 1980.

Reisner's book, like the one by Brooks, is a major contribution both as teaching material and as a reference. The emphasis in Reisner's book is on the regulation of the mental health professions and malpractice issues, while Brooks focuses more on civil and criminal commitment. Neither of these books enables the law student to learn psychiatric theories or treatment modalities in any depth; that is not their purpose. Instead, they cover the law, social policy, and ethical problems involved in the care and treatment of the mentally ill. This book, like the one by Brooks, aims to reach several audiences, but its main target is the law student.

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The Process of Divorce: How Professionals and Couples Negotiate Settlements, *by Kenneth Kressel. New York, Basic Books, 1985, 368 pp., $23.95.*

The basic theme of this book is that "there are many obstacles to a constructive settlement process—and many of

them have . . . to do with the difficulties and ambiguities of the professional role . . . [and] with the unhappy circumstances of the parties." Kressel is both a social psychologist who has been involved in research on divorce for more than a decade and a practicing therapist and mediator. The book integrates findings from his research, other research reports, and his clinical experience in a well-written and extremely useful overview of the participants and processes associated with divorce.

The book casts a critical eye on the popular attribution to lawyers, with their alleged adversarial orientation, of responsibility for the often debilitating effects of divorce while providing a somewhat too jaundiced view of the newest proposed panacea—mediation. Kressel does an excellent job of painting a good picture of the roles of therapist, lawyer, and mediator in divorce, using a set of research studies that he acknowledges is inadequate. Much of the findings come from the work of Kressel and his colleagues. One weakness of the book is that although he does recognize the methodological inadequacies of his data base (many of his results represent responses from very small numbers of subjects), he still paints his perspective forcefully.

Kressel does an extremely fine job of integrating materials from different sources to present cogent summaries of various issues, and he does so without the use of jargon. For example, he presents an excellent set of criteria for what constitutes a constructive divorce settlement negotiation and then looks at the spousal/situational and professional obstacles to achieving such a settlement. The spousal/situational factors include high levels of conflict, scarcity of divisible resources, elevated levels of stress and tension, disparities in relative power, and disparities in degree of interpersonal sensitivity.

A major factor in emotional power disparities is the fact that for the vast majority (75%–90%) of divorcing couples, the decision to divorce has not been reached mutually and at the same time. The consequence of this is that the spouses are not equally ready to engage in the arduous process of divorce settlement. One spouse is disadvantaged by not having resolved as much of the emotional trauma surrounding the divorce decision as has the other. Kressel urges the use of divorce counseling or therapy to permit both spouses to come to terms with the fact that the marriage is ending before negotiations over the terms of the dissolution begin.

Even if both parties to the divorce have achieved a reasonable level of readiness to divorce, other factors may interfere with achieving a constructive settlement. These factors include well-established and rigid patterns of destructive interaction, inexperience in the art of negotiating, complex issues involving the threat of loss of face or self-esteem, and social norms and institutions for conflict management that are weak or that unintentionally provoke destructive interaction. The professionals who assist divorcing couples have an unenviable task.

According to a group of therapists who do a substantial amount of divorce therapy and were interviewed in one Kressel study, the professional group that deserves the most opprobrium is divorce lawyers. This is unfair in Kressel's view. This book includes material on the results of a number of studies using the Lawyer Role Questionnaire. Responses from family lawyers suggested that lawyers could be broadly divided about equally into counselors and advocates. But even those lawyers with a counselor orientation, who favor a more psychological orientation to divorce rather than seeing the lawyer as a legal combatant and the client as a source of irritation and difficulty, have not had the kind of professional training that would give them the skills necessary to implement their preferred approach to divorce.

The general dearth of research on divorce is nowhere more evident than in the fact that Kressel could find no reports on what settlement negotiations actually look like when undertaken by lawyers. He emphasizes, however, findings that "perhaps as many as half or more of all divorcing couples do most of the settlement negotiations themselves, with only nominal assistance from lawyers." Given that clients have been shown to have inadequacies as negotiators, that lawyers play less of a role in divorce than formerly believed, and that even when they want to do so they are not professionally prepared to implement a psychological orientation to the process, some other method of helping clients with divorce settlement negotiations needs to be developed.

In the past decade just such a method has evolved—mediation. A nonpartisan third party—usually a mental health professional, sometimes a lawyer or layperson—helps the divorcing spouses work out a divorce agreement that ideally, is fair and workable. Unlike traditional divorce processes, mediation has already started to develop a body of research. Kressel is, to my mind (but I teach divorce mediation to teams of law and mental health graduate students), unduly critical in his evaluation of this research and of mediation. His intention seems to be to administer an antidote to some of the grandiose claims made for mediation in its infancy.

Kressel makes a strong case for the development of what he calls a therapeutic approach to divorce mediation. Therapeutic efforts include "all efforts on the mediator's part to explore, understand, and alter patterns of spousal communication, problem-solving, and conflict management which are manifestly interfering with a constructive negotiation process." Although this approach is contrary to that of O.J. Coogler, the founding father of divorce mediation, it is consistent with many of the approaches now emerging in mediation.

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Confessions of Son of Sam, *by David Abrahamsen, M.D. New York, Columbia University Press, 1985, 238 pp., $19.95.*

On Christmas Eve, 1975, a 14-year-old Bronx girl was stabbed repeatedly in the chest by an assailant who several years later would explain, "I wasn't going to rape her or take her money, I was only going to kill her. That's all" (page 89). So began a series of stabbings and shootings attributed to "Son of Sam." Most of the victims were young women parked with their dates. The police checked all current and former mental patients in New York State. Those of us responsible for forensic programs prayed he would not be one of our dischargees.

When "Son of Sam," David Berkowitz, was arrested in 1977, the Mayor of New York City went to see him. Berkowitz presented as an angelic, polite, pleasant, passive 24-year-old; he had no history of psychiatric hospitalization.

Immediately on his arrest, issues arose as to Berkowitz's competency to stand trial and whether he should be found not guilty by reason of insanity. Examining psychiatrists disagreed. One of the examining psychiatrists was David Abrahamsen, M.D., author of 13 books. On meeting Dr. Abrahamsen for the first time, Berkowitz said, "I know who

you are, you are Dr. Abrahamsen, I read your book *The Murdering Mind.* The book was good" (page 2).

Abrahamsen believes that "murder often begins at home." Berkowitz was adopted, and Abrahamsen says, "Adopted children, without exception, have in their innermost soul strong fantasies about their real parents, the biological family to whom they can give their love. Because being adopted is a circumstance not of their own making, they often withhold love from their adoptive parents; they are saving it for their true parents" (page 67). Furthermore, Abrahamsen believes that homicidal acts are tied to death wishes (Berkowitz said death was a "friend") and sex drives. According to Abrahamsen, "Symbolically, the closest he could come to adult genital sexuality was with knife and gun" (page 183). Berkowitz's hatred of women was reflected in a poem written a month after his first murder (page 87):

Old Mother Hubbard
Sitting near the cubbard [sic]
with a hand grenade
under the oatmeal.
Who will you kill now
Daughter of Satan?
In the image of the
Virgin Mary—pure and innocent
The Great Impersonator—
Is that you? "Yes."
How many have you decieved [sic]—
lured to slaughter like a fat cow?

Abrahamsen disagreed with the other psychiatrists in finding Berkowitz competent to stand trial and responsible for his acts. Abrahamsen explains but he does not excuse. The courts agreed with Abrahamsen.

In interviews with Abrahamsen and in more than 150 letters to him, Berkowitz seemed eager to please him. As Abrahamsen says, Berkowitz "would try to please me by telling me about matters that he, with his intuitive sense, felt I would like to hear" (page 224). Most of us like to hear that our constructs are correct. For Abrahamsen, Berkowitz provided such reflections.

Abrahamsen writes with clarity, facilitated by certainty. Not all of us have found murderers so easy to explain.

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HYPNOSIS

Life Reframing in Hypnosis: The Seminars, Workshops, and Lectures of Milton H. Erickson, vol. II, *edited by Ernest L. Rossi and Margaret O. Ryan. New York, Irvington Publishers, 1985, 328 pp., $39.50.*

This publication is the second edited volume of the seminars, workshops, and lectures of Milton Erickson. It emphasizes what are described as Erickson's naturalistic and utilization techniques, considered by the editors to be the essence of the Ericksonian approach. Erickson used the natural patterns he found in the behavior of his patients for the therapeutic purpose of reframing the problems. For example, if the patient's fists were clenched, he focused on the person's powerful grip; if bleeding, the patient heard Erickson tell him his blood was good and rich in color. Erickson attempted to harness everything occurring naturally in the patient's situation in such a way as to make it appear responsive to him (Erickson). He then went on to encourage the patient to revise his or her perspective on life and the problems, to "reframe" them, and to be responsive to the suggestions with therapeutic intent. The volume is filled with case reports, advice, and suggested techniques, many of which might prove helpful if the reader can integrate them comfortably into his or her own system.

I am not always persuaded, however, by Erickson's explanations and claims, many of which seem rather simplistic, nor by the ubiquitous interpretations of the editors of this book, who persist in attempting to justify intellectually every intuitive, spontaneous, and not always understandable remark of the master. Many, even among his critics, acknowledge that much of what Erickson said and did was probably therapeutic, even though we have little objective proof of that fact. The reasons for his effectiveness are less clear, but then we can rarely confidently account for the success of many other psychological procedures.

With regard to the editorial commentary, Rossi at one point wonders if Erickson would 'turn over in his grave if he could see how we are carrying on, labeling his humble, homespun tales with yet another level of phenomenological esoterica" (page 271). At least Rossi does not take himself seriously all the time. Let us take a look at another excerpt on pages 274 and 275: Erickson says to the patient,

> You are sleeping sufficiently deeply now so that if Dr. H were to snap his fingers, you could suddenly think that it was nighttime. You could go and turn on the light, and swear that you did not do it, because the turning on of the light would be a part of the thought. This is nighttime, and it would not be a part of your general conscious understanding that this is daytime. It would simply be an introjected form of activity.

The editors' comment on this is,

> What is the purpose of this curious posthypnotic suggestion for the subject to suddenly think that it is nighttime and turn on the light? When Erickson follows this up with the statement, "It would simply be an introjected form of activity," it really appears to confirm Ryan's view that he is using posthypnotic suggestion as a therapeutic behavioral exercise for rehearsing the introjection of spontaneous autonomous unconscious activity. . . . In this and the previous section he is giving posthypnotic suggestions to rehearse the possibility of the unconscious intruding spontaneously with its own therapeutic mechanisms. In this case he actually tells the subject that it is "an introjected form of activity." Usually he simply offered posthypnotic suggestions that functioned as forms of rehearsal for therapeutic work without the patient ever realizing it. This may account for the inexplicable quality of some of Erickson's work when both subjects and observers did not understand the implications and hidden rehearsals in Erickson's suggestions.

This example is not alone in the way in which it challenges the reader. If Erickson's work was at times inexplicable, his disciples in this instance are incomprehensible. For one who strongly asserted his atheoretical position, Erickson does not lack followers determined on buttressing his practices with theory.

As with so much in Erickson's work, the concept of a

limitless "unconscious" is clearly at the heart of much of what is discussed. Both Erickson and his editors make constant references to the omniscience and healing powers of this unconscious and spend much time trying to seduce it into carrying out its mission. The unconscious appears to be everything that is not immediately in the awareness, and much more. Somehow, left to its own devices and with encouragement, the unconscious will overcome just about anything. What should rightly be a metaphor is now being treated as a fact.

One is struck by the degree of scholasticism in much of the editorial comment in this book. It might be dismissed were it not for the knowledge that a whole cadre of individuals is being encouraged to administer treatment derived from this kind of theorizing, even though many of these individuals have little or no professional preparation to practice psychotherapy.

Few will deny the genius of Erickson as a healer and as an observer of human behavior. Some of his techniques are very useful adjuncts to the practice of psychotherapy. However, mixed in with his compassion and occasionally naive or confusing comments to patients are some rather provocative remarks and confrontative suggestions that would today challenge the ethics committees of our district branches were patients to complain about the use of such methods. A convinced body of theorists, each with his or her own emphasis, has now sprung from this atheoretical and paradoxical practice. Perhaps the time has come to ask the proponents of the various theories to disprove that theirs is a case of the emperor's new clothes.

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Multiple Personality, Allied Disorders and Hypnosis, *by Eugene L. Bliss. New York, Oxford University Press, 1986, 264 pp., $29.95.*

This book is stimulating and provocative. It devotes most of its attention to the concept of spontaneous self-hypnosis and the application of this presumed genetic endowment to various psychiatric syndromes and symptoms. Emphasis is placed on clinical observations regarding two very controversial topics in psychiatry: multiple personality and hypnosis. Since its introduction two centuries ago, reputable practitioners of hypnosis have had difficulty convincing other professionals that hypnosis has useful implications for the understanding and the treatment of psychiatric conditions. Similarly, the syndrome of multiple personality is a concept often looked on askance by psychiatry.

The first chapter gives a good but abbreviated review of the development, history, and nature of hypnosis. Dr. Bliss properly devotes considerable attention to the subjective nature of hypnosis, objections to the use of hypnosis in psychiatry, and problems of verifying hypnotic phenomena and claims. The historical overview is carefully documented and approached with scientific responsibility.

The section on contemporary hypnosis acquaints the newcomer to hypnosis by stating the basic assumptions of the current literature and provides a foundation for understanding the theory of hypnosis postulated by the author. Drawing on his knowledge of neural mechanisms and his clinical experience, Dr. Bliss formulates a theory that views hypnosis as a function of reticular activation. According to this theory, self-hypnosis, often induced by intolerable experiences, can produce psychiatric symptoms by manipulating functions of the neocortex.

Multiple personality is the example used to demonstrate the central mechanism of self-hypnosis and the insights that hypnosis can provide into the nature of psychiatric disorders. This presentation shows the integration and balanced judgment of a seasoned clinician. Relying heavily on standardized tests of hypnotizability, the author's study suggests that patients with multiple personality are excellent hypnotic subjects, that they may use self-hypnosis as a coping mechanism, and that they can often benefit from hypnotherapy. Dr. Bliss summarizes,

> The syndrome of multiple personality begins in childhood, usually as a defense against physical, sexual, or psychological abuse. The prime mechanism appears to be spontaneous self-hypnosis, which creates amnesias, an unconscious repository, personalities, and many other symptoms. (page 162)

This meaningful and realistic view of the interrelationship of hypnosis and multiple personality is followed by the questionable assertion that schizophrenia, sociopathy, posttraumatic stress disorder, anorexia nervosa, and the like may also be caused by self-hypnotic mechanisms.

Dr. Bliss is an entertaining writer who frequently uses interesting quotations. Patients' recollections of induced and spontaneous hypnotic experiences describe many hypnotic phenomena. In the final chapter, "The Patient Speaks," selected patients give firsthand reports of their experiences with multiple personality, self-hypnosis, and therapy. Although interesting and enlightening, these quotes provide only anecdotal support to the central theme of the book.

Because of early failures and disappointments with the therapeutic use of hypnosis, the author reports skepticism toward hypnosis for most of his professional career. This work reveals the process by which an experienced professional discovers the clinical utility of hypnosis, develops the professional skills of hypnotherapy, and integrates the technique into his treatment procedures. In summary, Dr. Bliss has produced a well-written book that should strengthen scientific acceptance of the concepts of hypnosis and multiple personality.

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Reprints of Book Forum reviews are not available.

Letters to the Editor

New American Board of Medical Specialties Publications

SIR: I write to call the attention of your readers to the publication of a new series of biographical directories of certified specialists. The American Board of Medical Specialties (ABMS), the parent organization of all certifying Boards, has published such a directory in each of the 24 specialties and also a compendium of all certified specialists. The *ABMS Directory of Certified Psychiatrists* (502 pages) was published in 1985 and includes biographical information on more than 22,000 Board-certified psychiatrists. In addition to the alphabetical listing of diplomates, there is a geographical index by state and city. The *ABMS Compendium of Certified Specialists* (published in September 1986) comprises seven volumes and 10,000 pages listing 337,000 Board-certified specialists in all fields. In addition to alphabetical specialty listings and geographic indexes, there is a master alphabetical index. These publications will be reissued every 2 years and represent the latest and most useful information on all certified specialists. APA members are encouraged to use this new reference work. Either or both publications may be obtained from the American Board of Medical Specialties, One American Plaza, Evanston, IL 60201.

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Smoking of Prescription Anticholinergic Drugs

SIR: Abuse of prescription anticholinergic drugs for their euphorigenic and hallucinogenic effects has previously been reported (1–4). Typically, abuse is by the oral route (4), and trihexyphenidyl tends to be favored (1), although abuse by other routes (1, 2) and with other anticholinergics (1, 5) does occur. The following case report describes anticholinergic drugs by intravenous injection and by smoking.

Mr. A, a 29-year-old unmarried, unemployed man, had had more than 30 previous psychiatric hospitalizations for schizophrenia and abuse of multiple substances, including marijuana, phencyclidine, heroin, amphetamines, and LSD. His schizophrenia, marked by auditory hallucinations, had been relatively stabilized by weekly injections of fluphenazine decanoate (25 mg) when he came to the psychiatric emergency room requesting a refill of a diphenhydramine prescription, which he had been given earlier for extrapyramidal side effects. The medical record revealed that Mr. A had previously abused trihexyphenidyl by the intravenous route, which had resulted in an infected abscess on his forearm. Consequently, his prescription had been changed and he had received either diphenhydramine or benztropine. When confronted with this information, Mr. A explained that the abscess had convinced him to stop injecting and to start smoking drugs. Two or three days a week over the preceding year, he had mixed 50 mg of diphenhydramine and 6 mg of benztropine with tobacco, rolled the mixture into a cigarette, and smoked it. This caused him to feel "speeded up," see fires erupting in his room, feel invisible, and have blurred vision. He also gave these cigarettes away on the street and told people they contained cocaine. He was advised against these practices and was told that the medication would be prescribed only for ongoing side effects of neuroleptic treatment. He was referred to his treating psychiatrist for follow-up.

This patient exhibited most of the diagnostic and demographic features reported for other abusers of prescription anticholinergic drugs (4). They tend to be young, male schizophrenic or sociopathic patients who are unmarried and unemployed and who abuse a variety of other substances. Mr. A's clinical features were also similar to those in other reports, including central nervous system stimulation and visual hallucinations (1–4). The visual hallucinations were in contrast to the auditory ones associated with his schizophrenia. An additional antihistaminic sedating effect, as might be expected with diphenhydramine, was not reported by this patient.

Although Mr. A had apparently been switched from trihexyphenidyl to benztropine and diphenhydramine because of their lesser potential for abuse, both of these drugs have also been associated with abuse (1, 5). To my knowledge, benztropine and diphenhydramine smoking has not been reported before, although the smoking of a mixture of trihexyphenidyl and tobacco by prisoners has (2). This patient substituted smoking for intravenous use, believing this to be a safer practice that did not sacrifice the immediacy and potency of effect. As the popularity of smoking other substances such as cocaine increases, clinicians should be alerted to the possible abuse of prescription drugs, including all anticholinergics, by this route.

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Neuroleptic-Induced Akathisia Treated With Pindolol

SIR: Recent studies have shown that the β blocker propranolol is a safe and effective treatment for neuroleptic-induced akathisia (1–3). No important effects on blood

pressure or pulse in patients with neuroleptic-induced akathisia but without cardiovascular disease have been noted for the dose range of propranolol studied to date (15–80 mg/day). However, certain patients are unable to take propranolol because of other underlying conditions, e.g., cardiovascular or pulmonary disease. We recently successfully treated a patient who had severe neuroleptic-induced akathisia and a sinus bradycardia (which precluded the use of propranolol) with the β blocker pindolol. We chose pindolol because this β blocker, unlike propranolol, has intrinsic sympathomimetic activity and therefore should not slow the heart rate as much as propranolol (4).

Mr. A, a 39-year-old schizophrenic white man, was admitted to the hospital because of an exacerbation of his psychosis. He had had numerous psychiatric admissions over the past 20 years, with a history of akathisia when taking various high- and low-potency neuroleptics. His psychosis had responded best to fluphenazine, but he had discontinued this medicine 1 month before this hospitalization because of complaints of restlessness. On admission to the hospital, Mr. A demonstrated paranoid delusions, auditory hallucinations, thought broadcasting, and thought insertion. He was restarted on a regimen of oral fluphenazine hydrochloride and developed akathisia, which increased in severity as the dose was raised to 60 mg/day. The patient's symptoms of continuous restlessness, pacing, and walking in place persisted in spite of trials of treatment with benztropine, 4 mg/day, and amantadine, 200 mg/day, plus lorazepam, 1.5 mg/day.

Mr. A's baseline blood pressure was 100/70 mm Hg, with a pulse of 50, which precluded use of propranolol to treat his akathisia because of concerns about worsening the bradycardia. The patient was started on pindolol, 2.5 mg orally twice daily. He reported an improvement in the akathisia within 1 hour after the first dose and on discharge showed a 50% reduction in both subjective and objective ratings of neuroleptic-induced akathisia (3).

To our knowledge this is the first case of neuroleptic-induced akathisia treated with pindolol. Pindolol is similar to propranolol in that it blocks both β_1 and β_2 receptors (nonspecific) and is relatively lipophilic (4) and so should exert activity on the central nervous system. However, pindolol, but not propranolol, has some intrinsic agonistic activity (acting either as a mixed agonist-antagonist or as a partial agonist). The effect of pindolol on neuroleptic-induced akathisia was similar to that reported with propranolol; it was rapid and occurred at a low dose. We found no indication that the partial agonist activity associated with this unusual β blocker exacerbated akathisia or limited the efficacy of treatment. Because of Mr. A's bradycardia, it was specifically this partial agonist activity of pindolol that allowed him to tolerate β blocker therapy. Thus, there may be a subgroup of patients who would be able to tolerate pindolol but not another β blocker. As this is a single case report, we urge further direct, controlled comparisons of pindolol and propranolol in neuroleptic-induced akathisia.

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Priapism Treated With Benztropine

SIR: We would like to report the case of a patient in whom episodes of priapism appeared to be associated with his dose of benztropine.

Mr. A, a 30-year-old black man, awoke from sleep with his first episode of priapism 2 weeks after his first treatment with a neuroleptic (thioridazine) began and the day after the dose had been increased to 200 mg h.s. Possibly relevant past history consisted of a head and back injury 1½ years earlier, not requiring surgery but with persistent L5/S1 radiculopathy. He was hospitalized, treated conservatively, and discharged 30 hours after the episode began, with his penis in semiflaccid condition; he recovered without sequelae.

Three years later, while being treated with an unknown medication, Mr. A began to experience daily erections on awakening that lasted several hours. A hemoglobin electrophoresis was read as hemoglobin A. Mr. A declined a recommendation for surgery, and after approximately 6 months the episodes ceased, again fortunately without residual impairment in sexual functioning.

For the next 5 years, while on various neuroleptic/anticholinergic regimens, Mr. A experienced no problems until chlorpromazine was discontinued and his benztropine dose was halved, leaving him on a regimen of trifluoperazine, 30 mg/day, and benztropine, 1 mg b.i.d. Within several weeks prolonged erections returned; eventually they were present virtually every morning when he arose, usually lasting 2–4 hours but occasionally longer and necessitating visits to an emergency room. His trifluoperazine was replaced by haloperidol, 5 mg t.i.d., but the episodes continued unabated. At this time the only other medications the patient was taking were occasional doses of diazepam and propoxyphene with aspirin for back pain—medications not suspected of causing priapism. He denied, and there was no evidence of, substance abuse. Sexual functioning with normal erections was still possible, but as this painful problem appeared to be getting worse, Mr. A began to discuss with the urology service the possibility of a penile implant. Despite his skepticism about benefiting from it, he agreed to try benztropine again, at a dose of 2 mg b.i.d. He reported dramatic improvement the next day and complete disappearance of the episodes within several more days, while not experiencing any interference with his ability to have normal erections and intercourse. He had no symptoms on follow-up 5 weeks later.

Priapism has been observed to be associated with a number of neuroleptics. This patient's first episode of priapism appeared to be causally related to thioridazine, with

recurrent episodes associated with a variety of other neuroleptics. We were able to find only one other report of priapism associated with haloperidol alone (1); two other reports citing haloperidol involved concomitant treatment with other neuroleptics (2). We found no previous report of priapism associated with trifluoperazine.

Inspired by a case report by Fishbain (3), who observed coincidental remission of priapism after intravenous administration of diphenhydramine for an acute dystonic reaction, and noting that Mr. A's recent recurrence of priapism might have been chronologically related to a reduced dose of benztropine, we took the opportunity provided by Mr. A to make our first, and thus far only, intervention of this type. Fishbain found only two other reports of medication-related acute priapism that responded to anticholinergic agents (both cases involved the use of benztropine; one of these subjects was a gelding) (4, 5). Our case seems to further support using trials of benztropine for prophylaxis of medication-related priapism in patients with such a diathesis.

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Clinical and Chemical Effects of Lithium Discontinuation

SIR: Many side effects have been associated with lithium treatment (1), including suppression of kidney and thyroid function and increases in serum calcium (2) and WBC (3). We have now extended previous results in a controlled study of lithium discontinuation.

As part of a study of the side effects of lithium discontinuation on neuroendocrine responses, six bipolar I patients (diagnosed according to Research Diagnostic Criteria) had a series of blood samples taken just before withdrawal of lithium and again 3 weeks afterward. The patients included two men and four women, with a mean±SD age of 56.5±9.2 years, who had been on a regimen of lithium prophylaxis for a mean±SD of 9.2±5.8 years at a level of 0.5–1.0 meq/liter. During the 3 weeks without lithium, the patients were seen weekly to determine their clinical status. Data collected included scores on a mood scale (1=most depressed, 7=most manic, 4=normal), presence of subclinical symptoms over the previous few weeks by self-report on the General Behavior Inventory (4) at the beginning and at the end of the study, and checklists of mood symptoms and side effects.

We found no significant change either in mood score (from 4.0 to 4.2) or in behavior score (from 9.3 to 10.5). As expected, there were significant increases in mean±SD thyroid indices: for T_3, from 27.8±1.6% to 30.8±2.7% ($t=4.24$, $p<.02$); for free T_4, from 2.53±0.45 to 3.15±0.72 units ($t=4.14$, $p<.02$); and for T_4, from 9.0±1.5 to 10.1±2.0 μg/dl ($t=3.09$, $p<.05$). For electrolytes, there were significant decreases in calcium (from 9.5±0.1 to 9.0±0.2 mg/dl; $t=5.42$, $p<.005$); magnesium (from 1.87±0.17 to 1.76±0.17 meq/liter; $t=3.18$, $p<.025$); and potassium (from 4.4±0.3 to 4.2±0.2 mmol/liter; $t=4.03$, $p<.01$). Both cholesterol and triglyceride levels fell: cholesterol, from 216.5±55.7 to 203.7±48.2 mg/dl; triglycerides, from 171.2±115.2 to 126.3±122.6 mg/dl ($t=3.80$, $p<.02$). There were significant decreases in WBC (from 7.5±2.2 to 5.4±1.0 thousand/mm^3; $t=2.62$, $p<.05$) and RBC (from 4.48±0.42 to 4.27±0.42 million/mm^3; $t=3.45$, $p<.02$). There were, however, no significant changes in sodium, BUN, and creatinine.

We believe that these results may indicate the reversibility of lithium's effects on thyroid, serum calcium, and WBC when the drug is discontinued. We have reported previously on the reversibility of lithium's effect on thyroid (5). The association of lithium withdrawal with reduction in blood cholesterol and triglycerides has not been previously reported but might be expected, considering lithium's effect of slowing metabolism and inducing weight gain (1). The successful completion of 3 weeks of lithium withdrawal without immediate relapse is consistent with the findings in our previous report (5) and indicates the safety of this procedure.

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Francis Bacon and *DSM-III*

SIR: David Faust, Ph.D., and Richard A. Miner, M.D., in "The Empiricist and His New Clothes: *DSM-III* in Perspective" (August 1986 issue), fault the rationale, strategy, tactics, and implementation of *DSM-III*, which they disparagingly call "quasi-Baconian." One infers that they favor the scholasticism which dominated psychiatry before *DSM-III*.

Now, human understanding of the universe has surely aggregated much faster during the four centuries since Francis Bacon than it did during the twice-four centuries of scholasticism that preceded him. On the other hand, one must concede that Baconian magic has failed with that vexing question, "How many angels can dance on the head of a pin?"

Perhaps I suffer from the rampant pragmatism that our authors deplore—and scanty faith.

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Dr. Faust Replies (copy to Dr. Sheeley)

Dear Sir Francis: Knowing you've been out of touch for some time, I'm writing to give you an update on some developments in scientific practice and philosophy. You will be happy to know that your scientific approach did prove to be an invaluable starting point in the evolution of methods for securing more definite knowledge. However, you would be amused and chagrined to discover that some members of my field (psychiatry/psychology) believe that science is practiced, or should be practiced, almost in the manner you originally outlined and that method has hardly advanced at all. Many embracing these views actually believe that *they* are current and that those who think or practice otherwise are outdated or antiscientific. Rest assured, however, that some of our greatest scientists have freely elaborated upon or extended your methods. Of course, such names as Newton, Darwin, and Einstein are unfamiliar to you. Anyway, they've done some OK things.

Many have shown unswerving faith—even blind commitment—to your idealized method. They dismiss or overlook the mountain of criticism and evidence that has virtually annihilated the last major remnant of your program—classical or logical empiricism—and they know little of contemporary or alternative views. I think you would find one of these alternatives most interesting and promising. It applies evolutionary concepts (whatever that is, huh?) to scientific knowledge development and argues that we should not work so hard to prove ideas, for supportive evidence can be found for almost anything, but rather should subject scientific propositions to rigorous tests. (This is a qualitative shift from your classic building-block model of knowledge acquisition, but you will undoubtedly recognize its true scientific spirit, for it even further reduces untested belief.) These tests help us to recognize and replace less promising ideas with better ones, and this process of self-correction protects scientific quality and promotes advance. Thus, disagreement or "inconsistency" among scientists is not always a bad thing, after all; rather, it ensures the intense scrutiny and testing that ideas require. I know this process is not as objective as you had hoped for, but we now realize we cannot entirely eliminate human judgment from science because, to date, science can only be performed by us humble humans.

I do not wish to disturb your rest, but I must vent some troubling thoughts. As you might infer, because scientific quality and advance depend on the open competition and exchange that fosters self-correction, we require an open marketplace for ideas. Stated differently, it must be the persuasiveness of the claims of scientific knowledge, and not the dictates of one group over others, that determines scientific choice and action. And yet my field shows an alarming tendency to instantly reject, belittle, and perhaps even sometimes suppress conflicting views about such fundamental issues as categorization and scientific method. This disparagement of alternatives, should it continue to grow and should it infect our new generation of scientists, might well stultify the open exchange of competing viewpoints, and all of us will be the poorer for it.

My comments may seem strange, but even one of your perspicacity cannot know that which he or she has not seen. Thus, a few references (1–5) are provided to help you catch up, and I will close with a statement by Mahoney (4) that summarizes my central points:

> Our knowledge emerges from collective exchange processes in which individual freedom is essential. Science requires relatively open windows. . . . The history of science suggests that progressive conceptual developments are very rare when these possibilities have been excessively constrained by foregone conclusions and restrictive epistemic policies. (p. 24)

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Your admirer,
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Failure of Nalmefene and Estrogen to Improve Memory in Alzheimer's Disease

SIR: Since Reisberg and associates' 1983 report of naloxone-induced memory enhancement in patients with dementia of the Alzheimer type (1), much time, money, and energy have been expended in efforts to replicate this finding (2, 3). Results of replication studies have been negative, including those in a previous report (4). Nevertheless, efforts to replicate continue, and it is important to report negative findings promptly.

We have recently suspended a pilot study of the effects of nalmefene and estradiol in dementia. Nalmefene is a potent, long-acting opiate antagonist that is structurally similar to naloxone and naltrexone. The half-life of nalmefene in plasma after intravenous, intramuscular, or oral administration is approximately 10 hours, with peak plasma concentrations reached 90 minutes after oral dosing.

Anecdotal accounts of partial responses to estrogen in dementia patients have also been reported. Much evidence exists that defines the interactions of endorphins and estrogens in the neuroendocrine system (5). In order to examine both estrogen and opiate antagonist effects in dementia, we began an open-label 4-week study of postmenopausal women with moderate dementia of the Alzheimer type (Global Deterioration Scale score of 4–5). These women were carefully screened with rigid inclusion and exclusion criteria. All had dementia compatible with *DSM-III* criterion 290.00 or 290.10, low scores on the Hachinski Ischemic Scale and the Hamilton Rating Scale for Depression, a Mini-Mental State score between 12 and 23, and the standard clinical features of dementia, ascertained by complete psychiatric evaluation. A medical history was taken, and a physical examination, an ECG, clinical laboratory tests, a CAT scan or nuclear magnetic resonance imaging, and a neurological examination were all given to rule out other causes of dementia, whether reversible or irreversible.

Five women entered the study. The procedure was fully explained to each patient and a relative, and informed consent was obtained from both. Each patient received 1 mg of estradiol each morning for 14 days. On day 15 oral

nalmefene was begun at the established dose of 10 mg b.i.d. On day 22 the estrogen was discontinued and the nalmefene regimen was continued alone until day 28, at which time the drug was stopped. An extensive battery of tests was administered weekly, including a clinical interview, the Hamilton depression scale, the Global Deterioration Scale, the Mini-Mental State, the Buschke Selective Reminding Test, the Trail-Making Test (lists A and B), the Digit-Symbol Substitution Test, the Word Fluency Test, the Brief Cognitive Rating Scale, and two relatives' rating scales.

One patient was dropped from the study in week 1 because of noncompliance. The other four completed the 4 weeks. Three showed absolutely no improvement while taking estrogen, nalmefene, or the combination. The other patient showed clinical deterioration during the study, beginning at week 2 and persisting until nalmefene was stopped. Within a few days this patient improved to baseline. She experienced considerable side effects from the nalmefene, including feelings of panic, nausea with loss of appetite, dysphoria, and headaches. These symptoms disappeared when nalmefene was discontinued. We suspended the study at this point because of the lack of efficacy and the emergence of major side effects.

Not only did this long-acting opiate antagonist fail to enhance memory in four patients with dementia of the Alzheimer type, but when it was given alone and in combination with estrogen, a reversible deterioration occurred in one of the four patients.

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Single Photon Emission Tomographic Brain Images in Dementia of the Alzheimer Type

SIR: Availability of ^{123}I-labeled bioamines, which are distributed proportionally to perfusion in normal brains, has allowed brain imaging with single photon emission computed tomography (SPECT), which is analogous to positron emission tomography (PET) but far less expensive (1). We used ^{123}I-labeled *N,N,N*-trimethyl-*N*-(2-hydroxy-3-methyl-5-iodobenzyl)-1,3-propanediamine (HIPDM), a pH change agent that crosses the blood-brain barrier (2), and SPECT to do brain imaging of 12 patients with dementia of the Alzheimer type (mean age=63.3 years) and five normal control subjects (mean age=69.4 years). The patients met *DSM-III* criteria, had a Hachinski score of less than 4, and had no evidence of secondary dementias. The control subjects were healthy and unmedicated and had no signs of dementia.

For brain imaging, subjects were given 5 mCi of ^{123}I-HIPDM (high purity) intravenously. After the subjects had spent 20 minutes in a darkened room, the imaging was done by a dual-headed camera. Tomographic reconstruction used a 30th-order moderate-cutoff (0.2 cycles/pixel) Butterworth filter. Brain images were divided into four types on the basis of a previous PET study (3). Cognitive and language tests were given to all subjects (4).

The images of the dementia patients were remarkably diverse: five showed bilaterally lower cerebral blood flow in posterior parietal areas (i.e., "typical" dementia images according to the PET study). The remaining images ("atypical" for dementia) included two that showed possible dementia (i.e., unilateral reduced cerebral blood flow in posterior parietal areas), two with multiple scattered focal areas resembling multi-infarct dementia, two that were normal, and one showing reduced cerebral blood flow in the frontoparietal area unilaterally. While SPECT did not misdiagnose any control subjects as having dementia, it misdiagnosed two clinical subjects with dementia as being normal.

The patients with the typical dementia SPECT images had significantly lower cognitive and language scores ($p<.018$) than the patients with the atypical dementia scans. The patients with normal images had higher cognitive scores than the other patients, but not as high as any normal control subject's scores.

The patients with atypical images were restudied a year later, and we found the following: two previous possible dementia images had progressed to typical dementia; one of the two normal images had progressed to possible dementia, while the other showed no change; one patient with frontoparietal cerebral blood flow deficiency showed no change; and two patients were too demented to undergo reimaging. All of these patients had deteriorated cognitively and clinically over the year.

HIPDM/SPECT images showed regional deficits in cerebral blood flow that were not revealed by the magnetic resonance imaging and CAT scans done in the neurological evaluation phase of the study. Earlier stages of cognitive dysfunction were associated with atypical scans, which over a year's follow-up may have progressed to typical or possible dementia scans. The fact that two patients with dementia had normal scans while they were clinically symptomatic—although their symptoms were not as severe as those of the patients with abnormal scans—supports the idea that SPECT imaging may not be sensitive enough to pick up the earliest brain changes. Whether PET can do so is still a moot question. Changes in SPECT images may follow other brain changes, which are only later followed by cerebral blood flow deficiencies, although the case of a patient studied by serial PET imaging suggests that these deficiencies precede symptomatic change (5). Too few patients have been followed by either technique to draw conclusions.

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Criteria for the Diagnosis of PTSD

SIR: Revisions proposed by the Work Group to Revise *DSM-III* (1) represent some potentially important changes in the diagnostic criteria for posttraumatic stress disorder. These include enumerating more clearly and extensively the symptoms seen in individuals with posttraumatic stress disorder and grouping the symptoms into better explicated, more homogeneous categories than does *DSM-III*. The proposed new criteria, however, may make it "easier" to diagnose posttraumatic stress disorder because of the addition of a fourth symptom under the B category of symptoms, which deals with persistent reexperiencing of the traumatic event. This fourth symptom, "physiologic reactivity or intense psychological distress at exposure to events that symbolize or resemble an aspect of the traumatic event" that precipitated the posttraumatic stress disorder (1, p. 99), appears to describe a conditioned phobic or anxiety response at least as much as it does a reexperiencing of the traumatic event itself (the three original symptoms in the B category for posttraumatic stress disorder in *DSM-III* are recurrent and intrusive recollections of the event, recurrent distressing dreams of the event, and sudden acting or feeling as if the traumatic event were recurring). Only one of the symptoms in this category, however, needs to be present for a diagnosis of posttraumatic stress disorder. Consequently, persistent reexperiencing of the traumatic event—in many ways the hallmark of the posttraumatic stress disorder diagnosis as it was originally conceptualized—would be altered under the proposed new criteria.

While phobic or anxiety responses following a traumatic event certainly are present in many patients with posttraumatic stress disorder, to include such symptoms in the "intrusive reexperiencing" category of posttraumatic stress disorder symptoms will, in our opinion, to some extent redefine the disorder. Patients whose symptoms after exposure to a traumatic event are primarily phobic with accompanying depression and/or anxiety may qualify for the diagnosis of posttraumatic stress disorder under the proposed *DSM-III-R* criteria but not under the current *DSM-III* criteria.

To informally test the impact of the proposed changes, we reviewed the cases of 16 patients from our practices who had been involved in relatively severe automobile accidents; each was involved in litigation over the accident and had been given a diagnosis of major depressive episode secondary to the accident. All of these patients also met the *DSM-III* criteria for posttraumatic stress disorder except for the presence of intrusive reexperiencing of the accident. Applying the proposed new criteria, we found that six of the 16 patients (37.5%) qualified for the diagnosis of posttraumatic stress disorder. Five of the six qualified because of the addition of the fourth symptom to the B category; the other qualified because of the expansion of the C category: "persistent avoidance of stimuli associated with the trauma or numbing of responsiveness" (1, p. 99).

Clearly, the proposed changes in the diagnostic criteria could have a considerable impact on decisions about which patients are given a diagnosis of posttraumatic stress disorder. While phobic-like reactions resulting from traumatic events may evoke recollections of the traumatic stressor in some individuals, it appears to us that the actual intrusive reexperiencing of a traumatic event is the hallmark of the posttraumatic stress disorder diagnosis, not a phobic or anxiety response per se.

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Neuroleptics, Prolactin, and Osteoporosis

SIR: Recent studies (1–3) have indicated that high prolactin levels in women are associated with early osteoporosis. All of the neuroleptics produce increased prolactin levels. To determine whether this is an area of concern, we did a pilot study of four patients who had been taking neuroleptics over a long period of time. These patients' prolactin and estradiol levels were determined, and they underwent a dual photon absorptiometry procedure. The results of the latter were compared with the Mayo Clinic series values, in which less than 0.965 g of bone ash per square centimeter was considered the fracture threshold. Measurements were done on the lumbar spine or the femoral neck. Our laboratory considers a normal prolactin level to be 0.0–15 ng/ml.

The two schizophrenic patients, ages 29 and 40 years, were regularly menstruating. Both had been on long-term neuroleptic medication. The 29-year-old had a normal prolactin level; the 40-year-old had a high level of 46.2 ng/ml. Both patients had densitometry readings above the fracture threshold. The other two (postmenopausal) patients had elevated prolactin levels but bone densities typical for their age.

From such a small group, only very tentative conclusions can be drawn. Clearly, even though some patients taking high doses of neuroleptics continue to have elevated prolactin levels, this does not necessarily result in loss of menstrual function, lowering of estrogen levels, or a reduction of bone density. It would be desirable to conduct a much larger study of this question.

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Mania Induced by Lithium Augmentation

SIR: In his letter "Rapid Switch in a Bipolar Patient During Lithium-Tricyclic Therapy" (October 1986 issue), Jeffery D. DeLisle, M.D., reported the case of a 39-year-old woman with bipolar depression who demonstrated a manic response when lithium was added to her ineffective regimen of imipramine, 50 mg/day. I would like to bring to the attention of Dr. DeLisle and other *Journal* readers two previously published reports of mania induced by lithium augmentation (1, 2). These reports described a total of four patients, two clearly bipolar and two with a history of unsustained hypomanic responses to tricyclic antidepressants during the current treatment episode. In three of these four cases, the tricyclic was stopped and treatment was continued with lithium and, in two cases, an added neuroleptic. In the remaining case, the tricyclic dose was not altered, but the patient's symptoms improved after reduction in the dose of lithium.

Since lithium alone does not produce mania, we agree with Dr. DeLisle that these observations provide support for the hypothesis that lithium might interact synergistically with mechanisms by which tricyclics alone can induce mania. While lithium augmentation appears to be a very useful and generally safe pharmacologic approach to the management of refractory depression (3), these observations should alert clinicians to the possible occurrence of this unusual adverse effect in patients with a bipolar diathesis.

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A Scale for Measuring Patients' Ability to Cope

SIR: Clinical experience teaches us that, while diagnosis guides treatment, we rely on our intuition to estimate a critical prognostic factor: the patient's resilience, adaptability, or healing capacity. Thus, the variability of clinical course within any diagnostic group of patients is often striking. The literature regarding the patient's point of view and coping capacity has emphasized the importance of giving up and the perception of having been given up (1).

We report here what appears to be a measurement of this or a similar complex, derived from the Welsh Anxiety Factor Scale (A) (2) and the Barron Ego Strength Scale (B) (3) of the MMPI.

From an outpatient psychiatric practice primarily oriented toward evaluation and consultation, we obtained 50 subjects whose T scores on the B and A scales (taking the former minus the latter, or B minus A, retaining the sign) differed by at least −4.0, noted their work status, and compared these with 50 randomly selected subjects from the same practice whose scores were −3.9 or above. Of the study group, two subjects were working ("work" is defined here as either out-of-home gainful employment or managing a household); of the control group, 15 subjects were working ($\chi^2=16.10$, df=1, $p<.001$).

We therefore conclude that in this group, the B minus A difference validly predicted nonfunction when a cutoff point of −4.0 was used. We are thus encouraged to carry out further studies to explore the possibility of a B minus A that could predict a subject's basic capacity to cope, regardless of diagnosis.

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Mandatory Outpatient Treatment

SIR: Dr. Paul Appelbaum's attempt in his editorial "Outpatient Commitment: The Problems and the Promise" (October 1986 issue) to downplay the significance of my paper "Posthospital Mandatory Outpatient Treatment" (in the same issue) is regrettable. Contrary to his assertion, I stated very clearly the variables on which my groups were matched. His desire that the groups be matched with regard to the number of previous admissions requires a standard that would prevent any evaluative research in this field. Picture state officials committing themselves publicly to a mandatory outpatient treatment law and then allowing a researcher to compel only half of those who qualify to be treated. Such discriminatory coercion is probably unconstitutional. Experiments in nature must use techniques different from those in the laboratory; we take the data where we find them. Dr. Appelbaum himself has reported uncontrolled data that have been subject to (as he puts it) "methodological constraints" (1).

However, we do not stop there. We attempt to control such variables by other statistical techniques. I addressed that problem in my paper in two ways. First, each patient served as his or her own control. Second, I showed that the degree of reduction of the recidivism rate was not related to the number of previous admissions. This technique is conceptually identical to that which Dr. Appelbaum used in one of his own studies (2). Perfect research? Of course not. However, it is an acceptable and reasonable statistical control of a variable.

If impossible standards like Dr. Appelbaum's are going to be set up, there will be no data. Those who enthusiastically endorse coerced outpatient treatment will not need to be encumbered by evidence.

Having downgraded the data presented, Dr. Appelbaum is now free to ignore the basic legal and social issues. Contrary to his assertion, I did not state that the Tennessee law on posthospital mandatory outpatient treatment is ineffective. I stated that the data failed to give evidence that the law is effective. This crucial difference is related to what in the law is called "the burden of proof." In our society, the right to be left alone has been called "the most comprehensive of rights and the right most valued by civilized men" (3). Posthospital mandatory outpatient treatment attenuates this right, and it should be abridged only if there is a compelling state interest (4). Perhaps the benefits anticipated by posthospital mandatory outpatient treatment comprise such compelling state interest, but the burden of demonstrating that the anticipated benefits are actually being attained falls not on those who urge caution but on those who advocate the law which abridges the fundamental right. Someone must demonstrate that the law works. My attempt failed to do so.

Perhaps future studies will show that the law can work. But until they do, psychiatrists should at least temper their therapeutic zeal and enthusiasm.

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Dr. Appelbaum Replies

SIR: Dr. Bursten's anger is unjustified. Although I respect his previous theoretical papers on forensic psychiatry and other subjects (and I am flattered by his extensive knowledge of my empirical work), I am afraid that the paper under discussion here is simply so flawed that no valid conclusions can be drawn from it. To say under such circumstances, as he does, that his study "failed to give evidence that the [outpatient commitment] law is effective" is a meaningless conclusion.

As I mentioned briefly in my editorial, the basic problem with the study lies in the selection of control groups. To compare committed patients at a group of four hospitals with those not committed at a fifth, as he did in his first analysis, is a dubious procedure, particularly when contextual factors are likely to be highly important in determining the success of outpatient commitment. Dr. Bursten's second comparison, between committed and uncommitted patients at the same hospital, makes more sense, but only if the two groups are similar on crucial variables—which in this case included previous rate of hospitalization, since rehospitalization rates were his major outcome criterion. Dr. Bursten did not match the patients on this variable, and his response to my comment on this subject suggests that he does not understand how such a match could be accomplished (nor, despite his assertion to the contrary, did his paper say on what variables the test and control groups were matched, although it did illustrate their comparability on several measures).

Nonetheless, Dr. Bursten claims that selection of appropriate control subjects is not an issue for his paper for two reasons. The first is that "each patient served as his or her own control." While this was true for his within-group comparisons, it was most certainly not true for his across-group comparisons, on which his conclusions rest. Second, Dr. Bursten claims that he "showed that the degree of reduction of the recidivism rate was not related to the number of previous admissions." If this were true, these would be useful data for establishing the validity of his comparisons. The data offered to support this statement in his paper, however, related only to the reduction in recidivism among the control patients in the only hospital in which outpatient commitment was *not* applied. This fails completely to answer the question of whether prior admission rates have an impact on the differential recidivism of committed and noncommitted patients in the hospitals (including the key hospital A) in which outpatient commitment was used.

Even if we ignore the problems with the selection of control groups, the underlying premise of Dr. Bursten's data analysis is fallacious. He assumes that his failure to confirm the findings of his first comparison with his second comparison must mean that the control hospital used in the first comparison was atypically bad at keeping patients out of the hospital and was therefore the cause of the difference in recidivism between committed patients and control patients (see his table 2). While that is one possible explanation, it is equally likely that the hospital used for the second comparison was atypically good at keeping all patients out of the hospital, thus washing out the positive effect seen for committed patients in the other three hospitals used in the first comparison. Dr. Bursten's inability to compare outcomes within his facilities, except for hospital A, makes any differentiation between these possibilities moot.

I have yet to read—much less produce—a perfect empirical study. I hold no one to such a standard. Rather, I ask only that studies be logically designed and clearly reported. A most commendable devotion to individual liberties is no substitute for these desiderata.

PAUL S. APPELBAUM, M.D.
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Globus Hystericus and Panic Attacks

SIR: In "Globus Hystericus Syndrome Responsive to Antidepressants" (July 1986 issue), Susan R. Brown and colleagues reported on three patients with fear of choking and difficulty breathing when they swallowed. All were successfully treated with antidepressants, i.e., imipramine, phenelzine, or tranylcypromine. The authors noted overlap but also dissociation between the globus symptoms and depression.

This is a very useful clinical contribution. The authors failed to comment, however, on a possible relationship between globus hystericus symptoms and panic attacks. Their first patient had a 1-year history of globus and a 50-year history of panic attacks and somatization disorder. In the second case, globus symptoms began when the patient had a panic attack while eating, which caused her to hyperventilate and fear that she might choke. She had a 20-year history of agoraphobia. The third patient had no history of panic attacks or agoraphobia. Concomitant with the globus symptoms, however, she complained of episodic

difficult breathing, which may have represented anxiety attacks.

I have seen a number of patients present with globus symptoms and a history of panic attacks. These patients have gained relief of both syndromes with pharmacotherapy for panic attacks, including tricyclics, monoamine oxidase inhibitors, and alprazolam.

Ms. A, a 39-year-old woman, complained of difficulty swallowing solid foods, leading to extreme weight loss. At age 19, she had choked on a sandwich, then started to have panic attacks characterized by dizziness, hot flashes, palpitations, and a fear of losing control. She lost her ability to drive a car and use public transportation. Swallowing difficulties and phobic features waxed and waned over the next 20 years, becoming worse at times of depression. Both phobic and globus symptoms benefited substantially from treatment with alprazolam, 6–8 mg/day.

Ms. B, a 20-year-old woman, started having panic attacks a year before seeing me. These were characterized by dizziness, pains in the chest, palpitations, and racing heart. Eight months later she began having difficulty swallowing, at first during exams but then in other situations. Her throat would get dry, and she became afraid to eat solid foods. There were no depressive features. Swallowing, panic, and phobic features benefited considerably from a regimen of alprazolam, 3–4 mg/day.

The association between panic attacks and globus hystericus could be coincidental. Alternatively, patients with panic attacks may be prone to overreact and be easily conditioned. Accidental choking on food, unrelated to panic, could for them become something to be greatly feared, leading to fear of swallowing. A third possibility is that occasional panic attacks while eating or swallowing might condition a subsequent fear of swallowing. Globus symptoms could also be due to the as yet unidentified biological instability thought to underlie other physical symptoms of panic attacks, such as tachycardia and dizziness.

At this point, further investigation of the association between globus symptoms and panic attacks is warranted. Globus hystericus may not always be hystericus.

MICHAEL R. LIEBOWITZ, M.D.
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Dr. Jenike and Associates Reply

SIR: We thank Dr. Liebowitz for his careful reading of our cases and his helpful comments. His points are well taken. We have not seen many more patients with these symptoms and cannot say from our small sample whether panic attacks are commonly associated. We might add that our patient 3 suffered from dementia and that her family were poor historians. It is possible that she also had a history of panic attacks; she certainly suffered from considerable anxiety.

Dr. Liebowitz outlines the histories of two patients with panic attacks and globus symptoms who responded to alprazolam in moderate doses. We have had difficulty weaning patients with anxiety disorders from alprazolam, and we prefer to use tricyclic antidepressants or monoamine oxidase inhibitors. If these are not successful, however, we would try alprazolam.

Clearly, more work is needed to elucidate the relationship of globus symptoms to depression and panic disorder. Until relationships are clarified, the prudent physician is still left with trying different medications for these patients. Since disability can be quite profound, as outlined in these cases, such patients should be aggressively treated with antidepressant agents even when depression or panic disorder is not part of the clinical picture.

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Boston, Mass.

Psychiatrists' Income

SIR: I thank Boris Astrachan, M.D., and Steven S. Sharfstein, M.D., for their interesting and informative paper "The Income of Psychiatrists: Adaptation During Difficult Economic Times" (July 1986 issue), which is a continuation of their many contributions in health care administration and economics. However, the numbers in the "percent change" column of table 1 are miscalculated. To use line 1 of that table as an example, they stated that a mean salary increase from $48,600 in 1973 to $99,500 in 1982 represents a 205% change. The 1982 salary was increased over the 1973 salary by a multiple of about 2.05; however, that does not translate into a 205% change. Change is calculated from a baseline, which in this case was $48,600. The increase to reach $99,500 was $50,900, which would be a change of just over 100% from the base of $48,600. That is, if a physician was earning $50,000 and later earned $100,000, his salary would have increased by a multiple of 2, but he would have had a 100% (not a 200%) change in salary. Stated another way, a 100% change (increase) in a $50,000 salary would produce a salary of $100,000.

A 100% salary increase over about 9 years would be produced by an annual salary increase of less than 8%. That is, if a given amount of money is left in a bank account that pays about an 8% annual interest rate for 9 years, it will double. An 8% annual increase is closely in line with inflation figures for many goods and services in our society in recent years, and I doubt that such an annual percentage income increase for physicians would lead to much negative attention. In fact, an average increase of about 8% is fairly low compared to recent inflation figures in many health care costs. Since a great deal of attention has recently been focused on health care costs and physicians' incomes, I would not want the salary change percentages, reported in table 1 as averaging about 200% during a recent 9-year interval, to go uncorrected and have the potential to be used against physicians.

TROY L. THOMPSON II, M.D.
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Dr. Astrachan Replies

SIR: Dr. Sharfstein and I are delighted that our paper was so carefully read. We agree with Dr. Thompson's analysis and conclusions.

BORIS M. ASTRACHAN, M.D.
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Thioridazine for Peptic Ulcer Disease?

SIR: It is beyond dispute that breakthroughs in therapeutics have been made by experimenting with nonconventional medications, and it is a fundamental principle of pharmacology that virtually no effective medication is without risk of adverse effects. But are the risks attendant to the use of antipsychotics worth the benefits of establishing their effectiveness in treating peptic ulcer disease?

In their letter to the Editor "Thioridazine in the Treatment of Endoscopically Proven Duodenal Ulcer Disease" (July 1986 issue), Ram K. Shrivastava, M.D., and Howard Siegel, M.D., reported on the successful treatment with thioridazine of three patients who had peptic ulcer disease. The rationale for trying thioridazine was not made clear; the authors cited its weak H_2 blocking properties and remained skeptical regarding any relationship between its strong anticholinergic effects and ulcer healing. No mention was made in any of the cases of standard resistance to treatment, and only one of the patients "experienced some psychiatric problems" at the time her ulcer disease emerged.

Although the doses used were relatively small (25–50 mg/day) and the duration of treatment relatively short (4–6 weeks), the practice of exposing nonpsychotic patients to the small but real risks of tardive dyskinesia, cardiotoxicity, and pigmentary retinopathy associated with the use of thioridazine (1–3) is questionable, especially given the availability of less toxic alternative treatment methods whose efficacy is well established. Particularly disturbing in this light is Dr. Shrivastava's and Dr. Siegel's "call for a double-blind, placebo-controlled study to prove the efficacy of thioridazine in the treatment of patients with peptic ulcer disease."

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Drs. Shrivastava and Siegel Reply

SIR: We appreciate Dr. Claman's response to our report and would like to make a few comments in reply to his letter. Dr. Claman cautions against treating peptic ulcer disease with thioridazine, a phenothiazine-group compound, since this drug carries the risk of tardive dyskinesia, cardiotoxicity, and retinopathy.

Dr. Claman's word of caution in such cases is certainly justified, and there is no doubt that this drug has the potential of producing these adverse effects. However, we were interested in treating these patients with it because they were partially refractory to treatment with available H_2 receptor inhibitors. Although this was not clear in our report, we were led to consider these patients partially refractory to treatment after we took into account the size of their ulcers and their recurrent relapses into ulcer disease while receiving other proven anti-ulcer therapy. In addition, one patient had intermittent psychiatric problems. Considering these factors and looking at the risk-benefit ratio and our previous experience with thioridazine, we were interested in treating this group of patients with this compound. We did not recommend using the antipsychotic dose of medication, but we felt comfortable with relatively small effective doses and short durations of treatment. We agree that it is somewhat premature to call for a double-blind, placebo-controlled study, but at this time it would indeed be valuable to have a control group, which should be considered as an obvious target for further research.

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HOWARD I. SIEGEL, M.D.
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Lithium-Responsive Depressed Patients

SIR: This letter offers additional analysis of data reported by Jesse Rosenthal, M.D., and associates in "Identifying Lithium-Responsive Bipolar Depressed Patients Using Nuclear Magnetic Resonance" (June 1986 issue). Their article's title suggests that nuclear magnetic resonance studies of red blood cells may identify a lithium-responsive subgroup of depressed patients. Their discussion was confined to differences between proton T_1 relaxation times of diagnostic subgroups of patients (bipolar depressed versus nonbipolar depressed). However, an interest in treatment outcome should direct attention to the differences between lithium responders and nonresponders, irrespective of diagnosis.

The authors' table 1 indicated that, after 1 week of lithium therapy, five lithium responders had mean±SD decreases in relaxation time of 20.4±5.3%, while three nonresponders had mean±SD decreases of 7.3±4.7%. If similar findings were obtained for a larger group of patients, then change in relaxation time could be used as a test for ultimate lithium response in depressed patients. Assuming that responders and nonresponders had the same mean±SD decreases as the eight patients Dr. Rosenthal and associates evaluated, and assuming that test results of both subgroups were distributed binomially, then a cutoff of 13.5% would distinguish nonresponders from responders with more than 90% specificity and sensitivity. (Other cutoffs could be chosen if either specificity or sensitivity were more important.)

Because response to antidepressant therapy often takes weeks, an early indication of ultimate treatment outcome could be of great clinical value. The report by Dr. Rosenthal and colleagues therefore suggests intriguing possibilities for assessing and planning treatment.

DOUGLAS MOSSMAN, M.D.
Charleston, S.C.

Dr. Rosenthal and Colleagues Reply

SIR: We agree with Dr. Mossman's observation that changes in proton T_1 relaxation times might distinguish lithium responders from nonresponders. During the project we informally speculated on a patient's responsiveness to lithium on the basis of the prelithium treatment T_1 time. Our predictions were usually correct.

Recent research on lithium's therapeutic mechanism has focused on transmembrane ionic transfers, intracellular-extracellular ratios, lithium's influence on ATP and GTP production, intracellular choline levels, and nonbiochemical

variables such as frequency and duration of episodes.

Although all of this is necessary research, it has yet to offer a clinically useful and economically feasible technique for predicting and monitoring lithium response. Variations in intracellular hydration, caused by molecular changes within the cell, can be measured with nuclear magnetic resonance and appear to correlate with behavioral variables.

A cell's internal environment is structured by its hydration status. Some depressed patients who respond to treatment with lithium have elevated proton T_1 times, which may be related to increased intracellular hydration. By implication, therefore, research should examine how intracellular water changes correlate with behavioral changes, and while the study of why a membrane alters its transfer and osmotic properties must continue, the intracellular response to unusual ionic conditions—in particular its stoichiometric changes and subsequent metabolic changes—must be explored. As Albert Szent-Gyorgyi said, when a fish gets sick, the last thing he thinks about is the water he is swimming in!

We are working to further define normal and abnormal parameters in a much larger sample. This includes the relationship of proton T_1 relaxation time and lithium response.

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Dystonia, Neuroleptic Dose, and Anticholinergic Drugs

SIR: Richard S. Winslow, M.D., and associates reported in the article "Prevention of Acute Dystonic Reactions in Patients Beginning High-Potency Neuroleptics" (June 1986 issue) that if acutely psychotic patients are started on high doses of high-potency neuroleptics (1,000–1,300 chlorpromazine equivalents daily), approximately half of them will develop dystonic reactions and that prophylactic treatment with benztropine diminishes the incidence of dystonic reactions to zero.

Another recent study (1) in which one of us (G.M.S.) participated similarly showed that high doses of haloperidol produced a 38.2% incidence of dystonic reactions in patients who did not receive anticholinergic prophylaxis. However, 11.5% of the patients who received anticholinergics also suffered dystonic reactions. In contrast, none of the 20 patients who received chlorpromazine, and who tended to be treated at lower equivalent doses (mean=558 mg/day), suffered a dystonic reaction.

Dr. Winslow and his colleagues referred to another study of the usefulness of anticholinergic prophylaxis by Hanlon et al. (2) in which no dystonic reactions were reported, even among patients receiving perphenazine alone, and suggested that the 2 days of pretreatment with phenobarbital that those patients received before entering the study explained the absence of dystonic reactions. We propose another explanation. Hanlon et al. (2) treated their patients with perphenazine at mean daily doses of 26.5 mg (the perphenazine-alone group; 27% incidence of all extrapyramidal side effects) or 21.2 mg (the perphenazine-plus-benztropine group; 10% incidence of all extrapyramidal side effects), i.e., 210–270 chlorpromazine equivalents daily. These authors noted that daily doses of perphenazine of 30 mg or more produced a significantly higher incidence of extrapyramidal side effects than lower doses.

All too often the question of how to use anticholinergic drugs properly is addressed before attention is given to how neuroleptic drugs are being used. We do not disagree with the proposition that high doses of neuroleptics produce a high incidence of extrapyramidal side effects and that prophylactic anticholinergic drugs can reduce that incidence. Rather, we wonder why such high doses of neuroleptics continue to be routinely used when all the studies that have attempted to demonstrate greater therapeutic efficacy of high doses than lower doses in the treatment of acute schizophrenia have been negative, e.g., the studies by Neborsky et al. (3) and Ericksen et al. (4).

We also question the "minimal anticholinergic toxicity" of 4 mg/day of benztropine. Psychotic patients do not usually speak eloquently about their subjective state, and self-rating scales completed during the first 1–2 weeks of treatment for an acute psychotic episode must be considered with caution. Normal volunteers and parkinsonian patients started on similar doses complain bitterly. In addition, recent studies (5) have called attention to the impairments in new memory acquisition that anticholinergic drugs produce at the doses routinely used by clinicians. This impairment of verbal learning of new material may deleteriously affect performance in a number of social and vocational situations and may vitiate the usefulness of psychotherapy or rehabilitation programs.

Until evidence appears that higher doses of neuroleptics, which produce more frequent and severe extrapyramidal side effects, offer additional therapeutic benefit, we recommend that lower doses (200–400 chlorpromazine equivalents daily) be used and that anticholinergic drugs be added if and when extrapyramidal side effects appear.

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Dr. Winslow and Associates Reply

SIR: The main point made by Drs. McEvoy and Simpson is that low initial neuroleptic dosage, rather than the use of prophylactic anticholinergics, is the better way to minimize acute dystonic reactions.

We have noted widely varying findings in the psychiatric literature about the correlation of dosage with the incidence and severity of early extrapyramidal side effects. For example, Drs. McEvoy and Simpson refer to two works that demonstrate the effectiveness of lower doses of haloperidol.

Ericksen et al. (1) stated that their higher-dose group "tended to have more frequent and severe" extrapyramidal side effects, but no specifics were given; Neborsky et al. (2) reported that 19 of their 20 patients suffered an extrapyramidal side effect during the 7-day study period, with no differences in severity or time of onset between the high- and low-dose groups—hardly an argument against prophylaxis.

Drs. McEvoy and Simpson surmise that the 20 chlorpromazine patients in the recent study in which Dr. Simpson participated (3) suffered no acute dystonic reactions because they were taking lower chlorpromazine-equivalent doses. In contrast, we believe that the result was due to chlorpromazine itself, which, like other low-potency agents, causes a low incidence of acute dystonic reactions because it is quite anticholinergic in its own right. Dr. Simpson and his associates (3) themselves made this point nicely by citing a study by Snyder et al. (4). There are even studies—e.g., that of Carter (5)—which suggest that higher doses of haloperidol may *protect* against early extrapyramidal side effects by exerting sufficient anticholinergic action. We conclude that the whole concept of using chlorpromazine equivalency is only valid when comparing antipsychotic potency and is invalid and misleading when assessing the relative likelihood of causing extrapyramidal side effects.

In our own study we attempted to assess the advantages versus the disadvantages of prophylactic anticholinergics. We do not claim that prophylaxis will eliminate acute dystonic reactions entirely. We do not claim that anticholinergics are completely without problems, especially with respect to prolonged use. However, we strongly disagree with the statement that "psychotic patients do not usually speak eloquently about their subjective state." Instead, we heartily agree with the words of Dr. Simpson and his associates (3): "Dystonic reactions are frequently frightening because of their abrupt and dramatic onset and can, on rare occasions, be life-threatening." Our experience both during our prospective study and afterward has been that psychotic patients, when offered an adjunctive medication that they are told may decrease the likelihood of an acute dystonic reaction, eagerly accept it and its possible risks of added anticholinergic symptoms. The most eager patients are precisely those who have themselves experienced or witnessed acute dystonic reactions.

Like Drs. McEvoy and Simpson, we generally support a policy of using the lowest effective neuroleptic doses for all patients. We might even consider a policy of using chlorpromazine itself, or other low-potency agents, for all patients for whom side effects such as significant sedation and frequent hypotension are not a barrier to adequate antipsychotic dosage. The fact remains, however, that high-potency neuroleptics have some advantages for many patients and that even in modest doses they appear to cause a substantial percentage of acute dystonic reactions.

Until consistent evidence appears that low doses produce a clinically insignificant rate of these reactions, we will continue to recommend that the safest and most humane approach is a brief course of prophylactic antiparkinsonian medication when one is starting patients on high-potency neuroleptics.

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Fear of Methadone Maintenance

SIR: In the article "Prevalence and Diagnostic Reliability of Methadone Maintenance Detoxification Fear" (June 1986 issue), Jesse B. Milby, Ph.D., and his coauthors described methadone maintenance detoxification fear as pathological. Their premise seems to be that apprehension concerning the possibility of recidivism reflects an "irrational expectation," which, they proposed, "can be modified with recently developed cognitive techniques."

It is difficult to understand the basis for this premise. The fact is that not one report in the voluminous literature on treatment outcome has ever made a credible claim that permanent abstinence from illicit narcotics after treatment for addiction (methadone maintenance or any other therapeutic modality) can be achieved consistently. And, sadly, that is a gross understatement!

Accordingly, the ethical responsibility of a clinician would seem to lie in reassuring the patient who contemplates detoxification that his or her fears are realistic and appropriate. Indeed, anything less would preclude obtaining informed consent before initiating a regimen that, under the best of circumstances, is associated with considerable risk of the most serious morbidity and even mortality.

In clinical terms, the goal of the authors might be described as the induction of an iatrogenic loss of reality testing capacity rather than cure of a "phobia."

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Dr. Milby and Colleagues Reply

SIR: Dr. Newman questions what he perceives as our basic premise that there is a pathological fear of detoxification which consists of apprehension about the possibility of recidivism. This represents a misunderstanding of our work. We *do not* assert that all fear of detoxification is pathological but rather propose that certain levels of realistic apprehension, anxiety, and concern about outcome are normal. We also propose that detoxification fear is best conceptualized as a continuum, with normal apprehension and concern about outcome placed at one end and considered to be within normal limits. Only reactions at the opposite end of the

continuum—those of severe anxiety, irrational ideas, fear of irrational symptoms, and phobic avoidance of detoxification in spite of objective signs of rehabilitation and a stated desire to be drug free—do we consider pathological.

Dr. Newman also asserts, "The fact is that not one report in the voluminous literature on treatment outcome has ever made a credible claim that permanent abstinence from illicit narcotics after treatment for addiction (methadone maintenance or any other therapeutic modality) can be achieved consistently." We think this statement ignores some important evidence of positive treatment outcome. While Dr. Newman may not accept that certain treatment outcome studies are credible or demonstrate permanent abstinence, there are several studies which demonstrate sustained abstinence after treatment. Duvall et al. (1) followed narcotic addicts tested at Lexington, Ky., and found that although most had used drugs soon after release, 32% had been voluntarily abstinent for 5 years after treatment. Vaillant (2) completed a 20-year follow-up of 100 addicts from New York City who were treated at Lexington and found that only 25% were still known to be using drugs and 35%–42% had achieved stable abstinence. After 12 years, 32% had achieved a minimum of 3 and an average of 8 years of abstinence, which was documented through multiple sources in the community. More recently, Simpson et al. (3) found that 61% of a random sample of 990 opiate addicts who had received treatment in community programs participating in a common federal data base had achieved abstinence for a year or longer before the follow-up interview.

We think that counseling patients who contemplate detoxification about the risks, and especially their readiness to be detoxified, is quite appropriate—indeed, recommended. However, unlike Dr. Newman, we do not think that all detoxification fear is realistic and nonpathological. We conceptualize patients who have met reasonable criteria for rehabilitation and wish to be detoxified yet who become extremely anxious at the mere thought of detoxification and avoid it as being on the pathological end of a continuum of detoxification fear. We suggest that such fear should be assessed and treated before detoxification is attempted.

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For-Profit Psychiatric Hospitals

SIR: Are for-profit psychiatric hospitals really as evil as Leon Eisenberg, M.D., implies in his commentary "Health Care: For Patients or for Profits?" (August 1986 issue)?

The title of his commentary seems to imply an either/or relationship between quality care and profit. Most psychiatrists are aware of nonprofit or government-run hospitals that provide substandard psychiatric care. Conversely, there are many examples of for-profit hospitals that deliver a high caliber of treatment.

Dr. Eisenberg complains about "cream skimming"—that is, for-profit hospitals treating only patients who are covered by insurance or who pay for their own care. How are hospitals to pay their staff if there isn't reimbursement? There is no free medical care. If psychiatrists, psychiatric nurses, and mental health workers provide conscientious service, they have the right to be paid.

The word "profit" has a bad connotation to some people, probably from the excesses of the capitalistic sweatshops of the past. If we update ourselves to 1987, however, we can view profits as one measurable criterion of successful treatment. With unfilled psychiatric beds across the country, the hospitals that "satisfy" patients will be successful; hospitals that do not will go out of business. Satisfying patients involves effective treatment, pleasant surroundings, and quality of care.

The profit motive inherently presents potential problems that need to be monitored. The businessmen running the health care corporations need strong input from psychiatrists regarding what is clinically needed to make the hospital successful, to attract patients, to satisfy referral sources, and therefore to make a profit. Why not let the marketplace dictate the cost-benefit ratio of various forms of treatment? Is more governmental regulation the answer?

Dr. Eisenberg's primary solution, national health insurance, is an interesting anachronism. Is it in patients' best interests to have government bureaucrats making decisions about appropriateness of treatment, fee schedules, and reimbursement? We have seen this work very poorly in the past.

Dr. Eisenberg seems a little out of step with the spirit of our country in 1987. His views echo the liberal ideas of the 1960s. This is nostalgic but not particularly pertinent to patient care and psychiatry in the 1980s and 1990s. Our country has recently developed a spirit of free enterprise, individualism, self-help, and responsibility. England, China, and some of the Eastern Block countries are experimenting with these ideas also, with encouraging results. Could it be that free enterprise and the profit motive are effective for improving society? With proper monitoring, could for-profit psychiatric hospitals deliver better treatment at lower costs and still give a reasonable return on investment to stockholders? Bright, responsible, and ambitious psychiatrists who are paid well for their services might be able to design and implement sophisticated new systems to treat psychiatric patients more effectively. They might actually be more creative and motivated than someone working on a fixed salary for a government agency or university.

Let the for-profit hospitals have their day. Monitor them. Check their quality assurance through the Joint Commission on Accreditation of Hospitals and through their yearly reviews by departments of public and mental health. Continue with the utilization review systems of Blue Cross, CHAMPUS, and other insurance companies. Track the for-profit hospitals' record in risk management in regard to lawsuits and patient abuse complaints. Let us reassure ourselves that they are delivering quality service at a realistic price. They might surprise us by performing far better than our old systems.

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Dr. Eisenberg Replies

SIR: I do not for a moment dispute Dr. Buck's contention that some voluntary and state hospitals provide care inferior to that obtainable in some investor-owned hospitals. I do not deny that mental health workers have a right to fair compensation for their services, nor do I regard investor-owned chains as an evil empire. My view is simply this: whereas the profit motive may be more or less effective for producing automobiles or steel (although the U.S. business record is hardly encouraging these days), it has no place in the provision of health care.

Dr. Buck would "let the for-profit hospitals have their day" in the hope that "they might surprise us by performing far better than our old systems," yet the evidence I reviewed in my commentary demonstrates no more than the growth of their stocks, and even that has begun to pale in the last year (1). Is profitability a suitable criterion for successful treatment, as he claims? Such a notion assumes that consumers are sophisticated enough to judge the quality of psychiatric treatment (as opposed to its amenities), a contention belied by everyday clinical experience. Dr. Buck dismisses regulation in favor of the marketplace but then concedes a need for monitoring. Who is to do that monitoring other than government or such private sector agencies as it empowers to act on its behalf?

The crucial question remains: what are the best means to ensure that psychiatric patients in need of care will receive that care when they lack the means to purchase it in the marketplace?

The experience of Canada provides an informative model. Canadian Medicare is an enlightened mixture of federal and provincial taxation to cover the costs of outpatient and inpatient care for all citizens. It is remarkably more effective than the hodgepodge now in place in our country: a mix of insurance schemes with highly variable coverage, means-based and age-based state and federal programs, and state mental hospitals. Our nonsystem leaves substantial segments of our population without coverage until they reach the extremes of penury. It entails disproportionately large administrative expenses (2). It threatens the fiscal integrity of teaching hospitals, the principal source of new knowledge and training for the next generation of physicians. Where is the evidence that the marketplace is responsive to *any* of these issues? Dr. Buck provides none.

He seems more concerned about tracing the political origins of my views than responding to the logic of my argument or the evidence cited in support of it. However, I will proudly grant him that my views "echo the liberal ideas of the 1960s"; indeed, I am prepared to trace them back at least as far as the New Deal of the 1930s. Despite their longevity, such ideas are neither nostalgic nor anachronistic; they provide the best means to ensure equity and quality in psychiatric care.

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Correction

In the letter to the Editor entitled "Fybromyalgia in a Woman With Bipolar Disorder, Manic Phase" (August 1986 issue, p. 1064) by Alice A. Hale et al., Dr. Wongsam (P.E.W.) is listed as a psychiatrist. She is a physiatrist, or specialist in physical medicine. The staff regrets the error.

Reprints of Letters to the Editor are not available.

APA Council Reports

At the fall component meetings of the American Psychiatric Association in Washington, D.C., on Sept. 10–13, 1986, the APA councils heard reports from their components. Following are summaries of the activities of the councils and their components.

The Council on Aging

Gene David Cohen, M.D., Chairperson

Geriatric psychiatry reached a critical milestone in 1986. In the past decade, the foundation has been laid for increased concentration on training, research, and treatment of psychiatric illness in old age: the National Institute of Mental Health established its Center on Aging, the National Institute on Aging was created, and the Veterans Administration set in place a series of Geriatric Research and Education Centers. It has been a decade marked by dramatic growth in the knowledge base of psychiatric illness in general and the special problems of the elderly mentally ill in particular—a knowledge base that, in increasing numbers of teaching facilities, is now being translated into specialized training curricula in geriatric psychiatry. In the main, an increasingly high level of academic excellence in geriatrics is being fostered in psychiatry, internal medicine, and family practice. The Council on Aging has sought to highlight the unique role of the psychiatrist, who works at the interface of the brain/behavior–body/behavior dichotomy that traditionally has artificially segregated disciplines.

In past years, the Council on Aging has focused on defining the role of psychiatry in geriatrics in terms of what distinguishes it from nonmedical disciplines, and the work of its past task forces has reflected that direction. However, biomedical and behavioral knowledge has expanded, critical financing issues have affected the role of psychiatry in treating the elderly, and other medical professions have increased their efforts to make their disciplines central to the treatment of the elderly. Therefore, council efforts have increasingly turned to better distinguishing the role of psychiatry from the roles of other medical disciplines in treating the complex set of medical needs of the elderly and to highlight psychiatry's role to practitioners, policy makers, and the public. The current complement of council work groups and task forces underlines the new focus of the council—a focus that increasingly requires council members and support staff to work with other APA components and offices to achieve mutually agreed-upon goals.

The council has worked with APA's Joint Commission on Government Relations, and at a joint meeting the council reinforced its belief that there is a critical need for APA to support congressional bills allocating funds for research, education, and clinical training in geriatrics. In addition, the council stressed the critical and continuing role of psychiatrists in both research on Alzheimer's disease and treatment of patients with the disease. Of equally pressing concern to the council are issues regarding mechanisms of third-party payment for the treatment of psychiatric illness in the elderly, predominantly Medicare and Medicaid.

Dominating council activity in the past year have been significant efforts to establish a "certificate of added qualification in geriatrics." This grew out of a meeting at which Maurice J. Martin, M.D., a member of the American Board of Psychiatry and Neurology, sought the input of the council on the appropriateness of establishing a formal subspecialty designation for geriatric psychiatry. A "certificate of added qualification" is substantially removed from the broader issue of subspecialization, but such a certificate for geriatric psychiatry would go a significant distance in demarcating the role of psychiatry in treating the seriously mentally ill elderly, a role increasingly sought by those in internal medicine and family practice. The result of these activities has been to encourage a wide-ranging debate in a variety of forums about the merits of subspecialization in general and what it portends for future directions in psychiatric training, research, and practice.

Work groups from within the council are actively engaged. One group, headed by Gary Moak, M.D., is completing a layperson's guide to psychotropic drug use in the elderly. Another group has revised a report on the psychiatrist's role in treating the elderly, which is now undergoing final reediting by Dr. Cohen. Yet a third group, under the aegis of Ken Sakauye, M.D., is developing a charge and scope of work for a task force to focus on the needs of the mentally ill ethnic minority elderly, a project which is to be undertaken in collaboration with members of the Council on National Affairs.

Outside of APA, the Council on Aging has continued its active liaison with the American Association for Geriatric Psychiatry, the National Voluntary Organization for Independent Living of the Aged, the Action Committee to Implement the Mental Health Recommendations of the White House Conference on Aging, and the National Council on Aging Board Committee on Physical and Mental Well Being. During the past year, the council sponsored an educational symposium at the National Council on Aging annual meeting and participated in a mid-decade evaluation of the implementation of the recommendations from the 1980 White House Conference on Aging.

The *Task Force on Nursing Homes and the Elderly Mentally Ill,* Benjamin Liptzin, M.D., chairperson, has sought information about programs and problems encountered by psychiatrists providing treatment to nursing home residents. This task force has been very active, preparing an annotated bibliography, presenting workshops at the annual meetings of APA and the Gerontological Society of America, and preparing papers for publication. As this report is prepared, the task force is about to submit to the council the results of its work, including recommendations for further action—af-

fecting training, public policy, and the role of the psychiatrist in nursing home practice. The council, in turn, will consider the need for further work in this area—an area in which psychiatry again is striving to establish its role and the scope of that role.

The *Task Force on the Interface of Psychiatry and Medicine in Geriatrics,* Marshal Folstein, M.D., chairperson, has presented its final report to the council. In view of the fast-breaking changes in this field, the council has decided to maintain this report as a council resource.

Building on issues related to financing the care and treatment of Alzheimer's disease, the *Task Force on Reimbursement Options and Alternatives in the Psychiatric Care of Older Persons,* Howard H. Goldman, M.D., chairperson, is developing a series of proposals to enhance opportunities for reimbursement for the treatment of mental disorders in the elderly. It will make a presentation at the 1987 annual meeting that will focus on means by which psychiatrists, now engaged in treatment of the elderly, can ensure that appropriate, full reimbursement for treatment is rendered.

Public policy on both the conduct of research on Alzheimer's disease and the clinical treatment of patients suffering from this disorder is at a critical turning point. The *Task Force on Alzheimer's Disease,* Eric Caine, M.D., chairperson, has engaged in a short-term project to develop a series of statements directed at other physicians, public policy makers, and the public that delineate the specific and crucial role of the psychiatrist in the management of Alzheimer's disease patients and in the conduct of research in this area.

Each of these task forces is engaged in part of the new delineation of the role of psychiatrists in meeting the research and treatment needs of the mentally ill elderly, a role that sets them apart from other physicians and nonphysician practitioners alike.

Members wishing to communicate with the council or to suggest subjects for its consideration are encouraged to contact Dr. Cohen through the APA Central Office and to attend the council's open meeting at the 1987 annual meeting in Chicago.

The Council on Children, Adolescents, and Their Families

Larry B. Silver, M.D., Chairperson

The council's various activities continue to be directed toward maximizing APA's effectiveness on behalf of the mental health needs of children, adolescents, and their families.

Active liaison efforts have continued with other APA components and with the National Consortium for Child Mental Health Services. The latter contacts had been made through Dr. Nancy Roeske, APA's able representative, until her death. The council will sorely miss these interchanges but counts on the continued effective liaison of Dr. Henry Work, who was appointed as APA's representative in May 1986.

Dr. Lawrence Hartmann represented the council on the APA Tri-Council on the Psychological Aspects of Nuclear Arms Development. This group's review of pertinent papers, programs, and reports of projects led to recommending the establishment of an APA standing committee that would study evolving nuclear arms issues and collect and disseminate pertinent information to the APA membership.

The council planned active collaboration with the Council on Psychiatry and Law on addressing the specific needs of children and adolescents in the development of the final draft of APA regulations on the "Right to Refuse Medication." It continued to collaborate with the APA Committee on Gay, Lesbian, and Bisexual Issues in developing an abstract for a session to be held at the 1987 annual meeting, "Homosexuality in the Family: Issues for the Psychiatrist."

Concern about the effects of violence in the media on the development of children and efforts to address the issue have continued through collaborative efforts with other organizations, APA's Joint Commission on Public Affairs, and APA's Office of Public Affairs.

Child and adolescent psychiatrists assigned to APA components met in September (during the fall component meetings) to discuss issues of particular concern to the American Academy of Child and Adolescent Psychiatry and the American Society for Adolescent Psychiatry. This assembly provided the opportunity for the entire group to be updated about National Institute of Mental Health (NIMH) programs related to children and adolescents, as well as the work of the APA components. The council again went on record as supporting efforts to assure National Service Corps assignments of child psychiatrists to facilities that provide services to children.

The *Committee on Chronically Ill and Emotionally Handicapped Children,* John Looney, M.D., chairperson, completed the manuscript of *Chronic Mental Illness in Children and Adolescents.* The publisher, American Psychiatric Press, Inc., expects that the volume will be available in the spring of 1987. The committee developed plans to generate advocacy within psychiatry through the establishment of liaison with NIMH, the American Academy of Child and Adolescent Psychiatry, the American Society for Adolescent Psychiatry, and the National Association of Private Psychiatric Hospitals. In their next efforts the committee will also address deinstitutionalization and its effect on all children and adolescents.

The *Corresponding Task Force on Confrontational Therapies,* Mark Blotcky, M.D., chairperson, reported findings from several site visits. The task force will continue to focus on the confrontational therapy applied in psychiatric residential and inpatient milieus as it completes its report.

The joint Reference Committee approved publication of the final draft of the report of the *Task Force on Changing Family Patterns,* E. James Lieberman, M.D., chairperson. The council expressed appreciation to the members of the *Task Force to Study Psychiatry and Child Abuse,* Virginia Wilking, M.D., chairperson, for their efforts on the task force report. The report of the *Corresponding Task Force on Reimbursement for Family Therapy,* William Beavers, M.D., chairperson, was received by the council at its September 1986 meeting. Each of the three components, having completed its task, was disbanded.

The *Task Force on Juvenile Justice Issues,* Edward Futterman, M.D., chairperson, held a meeting with representatives of the American Society of Adolescent Psychiatry, State Mental Health Representatives for Children and Youth, and NIMH, primarily to discuss the need for developing a handbook for psychiatric practice in the juvenile justice system. The group spoke with one voice about the need for such a volume. It is likely that formal recommendations will call for the preparation of the manual under the auspices of APA, with participation and cooperation from affiliated organizations. The task force has generated some information about the variability of relationships between mental health and juvenile justice systems at the state level. The final report will also deal with the need for modification of the core curricula of training programs.

It is anticipated that two new components, the Committee on Psychiatry and Mental Health in the Schools and the Committee on Family Violence and Sexual Abuse, will be activated in 1987 and that the council will also continue discussions about prevention and the effects of new technology (especially new forms of conception) on child development and child mental health. The council will hold a special meeting in January 1987 to explore these and other important areas as focal points for future activity.

The Council on Economic Affairs

Donald J. Scherl, M.D., Chairperson

During 1986 the council sharpened its focus on the major fiscal issues confronting psychiatry. Through the existing committees and task forces on prospective payment, quality assurance, financing and marketing, Joint Commission on Accreditation of Hospitals (standards and accreditation), and Social Security Disability Insurance, the council is able to address many pressing concerns. The council has also stimulated the establishment of two additional components to address the full spectrum of economic issues and policy formulation for the association. The new components are the Task Force on Future Trends in Private Insurance and the Task Force on Psychiatrist Payment. The council continues to foster nondiscriminatory mental illness insurance coverage, to collaborate with other APA components involved in carrying out educational programs for purchasers of health insurance, to articulate and promote fair and adequate standards of practice, to oversee the development and refinement of quality assurance programs, and to identify needs and resources for data related to these tasks. Stimulated by the Assembly, the report of the Commission on Peer Review, and the direction of the Board of Trustees, the council has taken on enlarged and more specific responsibilities for the quality assurance programs of the association. These programs will continue to be a major focus in 1987.

In addition to the assistance provided by the Office of Psychiatric Services, the council and its components look to the Office of Economic Affairs for major technical support of their activities. The Office of Economic Affairs involves itself in three kinds of efforts—gathering and disseminating information to a wide variety of people; special projects, such as involvement with the Task Forces on Prospective Payment Issues, Psychiatrist Payment, and Future Trends in Private Insurance; and technical assistance—for example, helping members deal with specific issues related to capitation. The office gathers information on psychiatric coverage and puts together information on trends and statistics. Among resource documents developed by the office last year were *The Coverage Catalog* and *A Status Report on PPOs*.

The following highlights from the components reporting to the council illustrate a most active year.

In March 1986 the Board of Trustees established the *Committee on Quality Assurance,* George Wilson, M.D., chairperson, under the council's supervision; this committee subsumed the functions of the former Committee on the CHAMPUS Peer Review Program and the Committee on Peer Review. The Board specifically charged the council with oversight of APA's quality assurance programs. The council recognizes the challenges presented by component oversight and by on-the-spot decision making by member and staff negotiators. The council and others face these challenges not only with the quality assurance programs but with the prospective payment issues, Social Security issues, and marketing issues—wherever APA has contracts or negotiations with external parties. Members of the new committee were appointed promptly, were oriented during the summer, and held their first formal meeting in September. During the fall component meetings, the council was joined for a half-day session by Dr. Wilson, several other committee members, and the director of the APA Office of Quality Assurance, Norman Penner. Among the matters reviewed were the revised CHAMPUS confidentiality procedures (including a compromise on "sanitizing" records for review) a bid to provide quality assurance services to a CHAMPUS demonstration project, and submission of a proposal to continue the CHAMPUS quality assurance programs. Also discussed was the extension of the current Intracorp preadmission inpatient program to include an equivalent review for outpatient cases. The council approved in principle the exploration of developing such a program and awaits completion of detailed plans for its study. During the formation of the quality assurance committee, the council served as a committee of the whole for oversight purposes. The council will continue to devote a major share of its time to this function and has scheduled an extra meeting for this purpose. The Committee on Quality Assurance has drafted, and the council has approved in principle, a mission statement. The committee also is developing specific responses to the report of the Commission on Peer Review. These documents will be reviewed during the council's winter meeting.

The *Committee on Financing and Marketing,* Howard Gurevitz, M.D., chairperson, proposed that APA's contract with GLS Associates for marketing/education on third-party reimbursement be extended for a third year. Both the council and Assembly endorsed this extension. During the first year of the contract, the committee and GLS gathered and analyzed information from members and district branches. This year the committee has overseen implementation of local seminars aimed at the private practitioner that emphasize evaluating opportunities in emerging alternative delivery settings (for example, knowing the issues to consider when one is invited to join a health maintenance organization). The committee wants to increase promotion and publicity for the seminars and explored with the council the possibility of local branch cosponsorship and/or cost sharing. The committee is now working with several district branches to determine what local staff is needed to effectively deal with industry and the general health care field. This will give the committee a clearer idea as to what type of technical assistance the national project should develop or promote. The committee also plans to encourage development of a network of expertise or information exchange among the district branches. In addition, the committee continues to collect data and, through this effort as well as the seminars, is developing a number of useful informational materials.

The council asked the committee to consider how the new task forces might use the work it has done and the data it has collected, i.e., information on mechanisms of payment, different practice styles and factors that influence income levels, and economic decisions made by psychiatrists as they select styles of practice.

The *Committee on Interprofessional Affairs,* Mildred Mitchell-Bateman, M.D., chairperson, serves as the APA liaison to the Joint Commission on Interprofessional Affairs. The commission is a consortium of representatives of APA, the American Psychological Association, the American Nurses' Association, and the National Association of Social Workers. Annually two elected officers and the executive director of each of the four organizations attend a leadership conference. Agreements reached during the 1986 conference included the following: 1) each of the four organizations will make it a high priority to intensify internal commitments and efforts to present differences and disagreements in a collegial manner, 2) statements formulated by the organizations will reflect a respect for one another's integrity and autonomy, and 3) each organization will strive to present data in support of its positions accurately and fairly. In addition, attempts will be made by the chief executive officers of the four organizations to meet more regularly. APA will host the 1987 leadership conference.

The Joint Commission on Interprofessional Affairs has developed *Guidelines for Interprofessional Relations,* which are now available on request from each member organization. Further, representatives from each organization are developing a statement defining the role of their discipline.

The *Committee on Hospital-Based or Hospital-Related Psychiatric Services,* Gerald Flamm, M.D., chairperson, reviewed the alcohol and drug abuse standards proposed for inclusion in the *Accreditation Manual for Hospitals* and *Consolidated Standards Manual* of the Joint Commission on Accreditation of Hospitals (JCAH). The committee passed on to the JCAH its proposal to substitute more appropriate medical language in place of the language proposed by the JCAH. The committee commended the JCAH task force on drug

and alcohol standards for its development of the principles on which the standards were based. The committee noted that the proposed standards reflected the overprescriptive characteristics of the *Consolidated Standards Manual.* Having circumvented this overprescriptiveness by encouraging the JCAH to survey hospital-based psychiatric services under the *Accreditation Manual for Hospitals,* the committee will watch for trends toward overprescriptiveness in future proposed standards.

Development of the alcohol and drug abuse chapter renewed the committee's consideration of whether standards for psychiatric services should be presented in a single chapter rather than scattered throughout the manual. While there is obvious appeal in a separate chapter, there is even greater appeal in psychiatry's integration into medical care along with other medical specialties. The committee will continue to consider this matter.

The *Task Force on Social Security Income/Social Security Disability Insurance (SSI/SSDI),* Arthur Meyerson, M.D., chairperson, called attention to events beginning in April 1985, when the Health Care Financing Administration (HCFA), through policy letters to Medicare intermediaries, instigated a series of denials of Medicare payments for partial hospitalization. The denials were made on the grounds of "inappropriateness of care provided" or "the care is designed to maintain the patient rather than bring about active improvement in a reasonable period of time." Task force members, staff of the Division of Government Relations, and representatives of the American Association for Partial Hospitalization and the American Hospital Association have met with the HCFA staff several times. The Medical Director wrote to the administrator of HCFA suggesting intervention in assessing the current confusion.

Dr. Meyerson and staff of the Division of Government Relations also met with staff of Senator Heinz, Select Committee on Aging, to explore new Medicare initiatives in day treatment. There was no congressional action this year; however, the task force and council will closely monitor how this matter is taken up in the 100th Congress.

APA has succeeded in filling much of the Social Security Administration's SSDI state agency needs for psychiatrists as consultants for reviewing cases. APA members were notified of these needs through *Psychiatric News* and individual district branch contacts. This is a recurrent need. The task force continues to share its information on the APA/SSDI project with the Council on Research.

The *Task Force on Future Trends in Private Insurance,* Robert Gibson, M.D., chairperson, was established in December 1985 to predict future trends in private health care insurance and their implications for psychiatric benefits. As major restructuring in health care delivery evolves, payment mechanisms, including private health insurance, change in corresponding fashion. No other APA component has this specific focus, although many components within and outside the council have concerns related to various aspects of health care insurance.

To fulfill its charge, the task force will first identify various factors and trends relating to health insurance and financing mechanisms. Second, it will speculate on the consequences of these factors and trends. Third, it will develop a system to collect data early and to update them. By means of this synthesis and analysis, the task force should be in a position to identify issues it should pursue and to identify potential tasks for other components. The council recognizes the necessity for contact and coordination with other components if APA is to avoid speaking divergently on insurance issues.

The *Task Force on Psychiatrist Payment,* Boris Astrachan, M.D., chairperson, was established in the spring of 1986 and held its first meeting in September. The task force has two goals: first, to understand the various potential mechanisms for funding a practice and their implications for whether the psychiatrist eventually receives fair fees for the services delivered, and second, to determine the methods and value scales that will be most useful in defining the activities that form the elements of current psychiatric practice. The task force hopes to begin to collect data on such things as practice patterns to get a sense of how money is allocated and spent, how people are paid, and how to obtain payments from the insurers. The council has asked other components and individuals to share information with this task force to supplement the data it collects.

The *Task Force on Prospective Payment Issues,* Joseph T. English, M.D., chairperson, continued to outline for the association the evolution of the rapid shift from cost-based retrospective reimbursement to prospective payment for health care. This marks the dawning of a new era in American medicine, which includes prospective payment for Medicare patients based on diagnosis-related groups (DRGs). Prospective payment presents incentives and disincentives for health care providers that may or may not be desirable for patients, hospitals, or practitioners. Having established in its previous years' studies that DRGs are an inadequate approach to prospective payment, the task force is exploring potential alternative payment mechanisms. Certain issues cut across the range of possible mechanisms. For the time being, the exemption from DRGs for many psychiatric facilities continues.

The council and task force, in concert with the Office of Economic Affairs and others, sponsored the leadership conference "Prospective Payment: Implications and Issues for Psychiatry, Patient Care and the APA." Experts from both within and outside the organization addressed approximately 80 participants at the meeting in February 1986. The council was pleased with the positive feedback from participants and APA officers. Details of the conference may be obtained from the Office of Economic Affairs.

The Council on Internal Organization

Ronald Shellow, M.D., Chairperson

The council monitors "all those matters involved in the organizational structure of the Association not covered by constitutional committees." There are 11 components that report directly to the council and 16 components that report to committees under the council. As a result, the council oversees a wide range of activities, such as the program content, exhibits, and arrangements for the annual meeting; the benefits offered to APA members, such as insurance and retirement programs; the maintenance and care of APA-owned properties; data processing and other information systems within the Association; the various prizes and awards presented by the Association for outstanding achievement; and all personnel and staff benefit programs, such as compensation mechanisms, insurance coverage, and retirement and pension plans.

The council has been extremely active during the past year, particularly with the annual meeting, member benefits, policies regarding publication of reports developed by APA components, and the grants and awards program.

The *Scientific Program Committee,* Robert Hales, M.D., chairperson, reported the success of the 1986 annual meeting, held in Washington, D.C. The total registration was the second highest in history (12,421), and a record number of APA members attended. The meeting generated the most income ever. The committee looks forward to an equally successful annual meeting in Chicago in 1987. The council approved certain recommended changes for this meeting. The meeting will end on Thursday, and Friday will be reserved for visits to various institutions. The opening session will be held on Sunday afternoon from 5:00 to 7:00 p.m., and the annual business meeting will be Monday afternoon from 12:30 to 2:00 p.m.

The *Committee on Advertisers and Exhibitors,* Henry Work, M.D., chairperson, works closely with the companies and organizations that advertise in APA publications and purchase exhibit space at APA meetings. Because of the outstanding success the committee has had in working with exhibitors, in the future it will focus more intensively on its relationship with advertisers. The council approved committee recommendations to increase funds for commercially sponsored symposia, to close the exhibits for the week on Wednesday evening, to extend exhibit hours to 8:00 p.m. on Sunday and to 5:00 p.m. on the other days, to relax the policy regarding gifts from exhibits but include regulations to preserve the dignity of exhibits at the annual meeting, and to ask the Board of Trustees to assist in maintaining standards for exhibitors.

Alan Levenson, M.D., APA Treasurer, is chairperson of the *Committee on Grants and Awards.* The committee continued to organize and standardize policies concerning the awards program. Steps were taken to obtain funding for a new award for schizophrenia research, to refine the guidelines for the APA/Pennwalt Resident Research Award and the media awards, and to create the new Jacob Javitz Public Service Award.

Paul Slawson, M.D., chairperson of the *Committee on Professional Liability Insurance,* was thanked for his work with the committee over many years. The committee was terminated; its functions have been taken over by Psychiatrists' Mutual, which will report directly to the Board of Trustees.

The *Committee on Member Life, Accident, and Health Insurance,* Harvey Bluestone, M.D., chairperson, continues to work at resolving differences with the former carrier and bringing efficiency into the present program. The committee reported that it was impossible to claim a training analysis as a health benefit and still claim it as a purely educational benefit. The major medical insurance plan will require a substantial premium increase for the next policy year.

The *Committee on Special Benefits Programs,* Abram Hostetter, M.D., chairperson, recommended a new plan for automobile rental discounts through National Car Rental and a travel program through First Travel Service. It continues to investigate ways to improve the members' retirement plan. The committee plans a series of seminars on computers in psychiatric practice.

The *Committee on Information Systems,* Leigh Roberts, M.D., chairperson, oversees policy concerning the Association's use of telemedicine, information systems, and related systems. The systems work well with extremely efficient work by a small staff. Telecommunication systems for key officers are in place. The committee has one component reporting to it, the *Subcommittee on Telemedical Services,* Jane Preston, M.D., chairperson. The subcommittee is promoting a new technology—the use of interactive videos for medical delivery. In addition, it is working on the ethical and legal issues associated with such medical delivery. Telecommunications is now seen as a practical way to provide medical expertise to those who would not otherwise receive it.

The *Personnel Committee,* William Sorum, M.D., chairperson, has been extremely active in developing a revised personnel manual and an affirmative action program. Through one of its members it has been exploring and solving certain staff difficulties.

The *Committee on History and Library,* Lucy Ozarin, M.D., chairperson, has been preparing exhibits and articles and supporting the new Marion Kenworthy Learning Center in the APA library. The committee has proposed sponsorship of a monograph series, "Portraits in Psychiatry." The committee and the council are also supporting increased funding for the APA library.

The *Committee on Friends of the APA,* Cynthia Rose, M.D., chairperson, is currently drafting new bylaws for the umbrella organization for affiliated groups.

The Resource Development Committee asked the council to review a proposal to establish an office of development and an APA foundation. The council supported the proposal in principle.

In addition to working with these components, the council, in association with the Elections Committee, looked into the relationship between the Central Office and district branches. It also discussed at great length implications of the moves toward subspecialization in psychiatry and implications of the AMA's health policy agenda for our specialty.

The Council on International Affairs

Harold Visotsky, M.D., Chairperson

This council works closely with the Office of International Affairs in monitoring the coordinating aspects of psychiatry that have international implications. In addition to overseeing and assisting the specific work of the components reporting to the council, outlined later in this report, the council and the office serve as a clearinghouse for international contacts and referrals abroad. A number of APA members have benefited from these contacts and referrals, and colleagues from many other countries have received assistance for such exchanges, including Australia, New Zealand, Brazil, the People's Republic of China, Korea, West Germany, Poland, England, Kenya, Nigeria, Venezuela, Canada, Chile, Finland, Japan, Spain, Guatemala, Iceland, Norway, Egypt, Hong Kong, Lebanon, Mexico, South Africa, India, the Netherlands, Denmark, Peru, and Greece.

The council, as well as other APA components, has expressed its grave concern over the United Nations Sessional Working Group report on persons detained on the grounds of mental ill health or disorder, which has been published in a preliminary version for the United Nations Human Rights Commission. The document is believed to be strongly antipsychiatry and unrealistic in its depiction of current psychiatric practice. Dr. Visotsky and the chairperson of the Council on Psychiatry and Law formed an ad hoc working group, at the request of the joint Reference Committee, to redraft the report so that it could be sent to the Institute for Human Rights in Geneva by mid-December and be placed on the agenda for the Human Rights Commission at its meeting in February. The working group also had representation from the Assembly of District Branches. The council and the Office of International Affairs were to facilitate the distribution of APA's concerns and comments to psychiatric organizations in other countries, encouraging them to have input into their foreign ministries as well.

The council is concerned about certain misperceptions that have arisen as to APA's contact with our colleagues in the Soviet Union. The council has proposed that APA adopt the position of encouraging APA members to have scientific contacts and collaboration with colleagues in the Soviet Union as long as they do so individually and not as members of APA components. The council has asked the Board of Trustees to take the position that official contact between APA and the All Union Society of Psychiatrists and Neuropathologists of the Soviet Union can be established only if it includes the opportunity for discussion of abuses of psychiatry in that country.

The council is recommending that a task force on terrorism be established for 1 year. If approved, the task force would be charged with studying the definition and scope of terrorism and what role, if any, psychiatry can play in these issues.

APA's role in the study of the psychological aspects of nuclear arms development has been reviewed by the three-person Tri-Council on the Psychological Aspects of Nuclear Arms Development, chosen from the membership of the Council on International Affairs, the Council on Children, Adolescents, and Their Families, and the Council on National Affairs. A proposal for the establishment of a task force has come from this group. The council supports this proposal and has suggested that this work be monitored by the Council on National Affairs with liaison representation from the Council on International Affairs.

The council continues to be gratified by the response to the International Scholars Program for the annual meetings. The individuals chosen for 1987 are from India, West Germany, Greece, Poland, and the United States. This format has provided a broad exposure to international perspectives for all participants at the annual meetings and has been well received. In addition, the council continues to encourage donation of books and journals to individuals in countries where psychiatric literature is not readily available.

The *Task Force on Problems of Americans Overseas,* Eric Plaut, M.D., chairperson, organized the successful conference "Living Abroad: Adjustments and Crises," which was held Oct. 9–10, 1986, in Washington, D.C. The conference was cosponsored by the American Bar Association and the U.S. State Department. The following plenary sessions were presented: "Problem Definition: The Stress of Unfamiliar Problems, Unfamiliar Resources, and Unknown Support Systems," "Physical and Emotional Challenges of the Overseas Environment," "Living with the Threat of Terrorism," "The Family Crisis: Relocation Abroad," and "The Family Crisis: Relocation to the United States." Workshops focused on legal issues; employer, managerial, and personnel issues; exotic and ordinary medical problems; mental health issues and alcohol and drug abuse; culture shock, ethnocentricity, and cultural adaptation strategies; and family issues for singles, spouses, children, and significant others. The conference participants were employees of the U.S. government, multinational corporations, or nonprofit organizations and private individuals working in this area. A network of organizations and individuals has been established, and the evaluation by the participants indicated a strong desire for annual conferences of this type. The task force will consider the next steps and make suggestions to the APA leadership. All expenses incurred in this conference were covered by registration fees and outside funding.

The *Task Force to Plan the Joint Meeting With African Colleagues,* Ezra E.H. Griffith, M.D., chairperson, was pleased with the outcome of this conference, which was held in Nairobi, Kenya, Aug. 10–14, 1986. The meeting, titled "Psychiatry in Africa and the Americas Today," was cosponsored by the Black Psychiatrists of America and the African Psychiatric Association and was dedicated to the late Dr. Andrea Delgado. Dr. Delgado was a former president of the Black Psychiatrists of America and the first chairperson of the American task force that planned this meeting with the Africans. She died in 1984 after a long illness.

During the conference, distinguished lecturers from Africa, North America, and the Caribbean presented papers on the problems of chronic patients in the United States and Africa, current trends in American and African psychiatry, historical evolution of African psychiatry and the history of black psychiatry in the United States, and problems in psychiatry in African countries and the Caribbean. Simultaneous paper sessions were presented on subjects related to clinical psychiatry, traditional and Western values in psychiatry, identity development, forensic psychiatry, alcohol abuse, substance abuse, resources and payment mechanisms, psychiatric education, family, psyche and soma, children and adolescents, somatic treatment, mental health and human rights, community psychiatry, clinical and research advances, health care systems, and ethnicity and psychiatry. The expenses incurred in this meeting were covered by registration fees.

There will be a workshop at the 1987 APA annual meeting in Chicago on issues that arose at this conference.

The *Committee on International Abuse of Psychiatry and Psychiatrists,* Michael Zales, M.D., chairperson, continues to work on behalf of many victims of abuse in a number of countries. The committee is part of a growing network of associations and human rights organizations that are concerned about these issues. The committee has encouraged many of these organizations to take up the cause of Dr. Anatoly Koryagin, an APA member imprisoned in the Soviet Union, who is interned because of his activities in opposition to the use of psychiatry for political purposes in that country. Even though a number of cases from various countries are received by the committee, the large majority of these cases involve the Soviet Union. The committee has encouraged the APA leadership to take a position regarding collaboration with that country in light of these abuses. The committee encourages individual contacts and collaboration with individual psychiatrists in the Soviet Union because it realizes that the abuses are perpetuated by a small minority of our colleagues there.

The committee has been quite concerned about the findings of a delegation from the International Commission of Jurists indicating a possible abuse of patients' rights in Japan. It appears, however, that the Japanese government has moved rapidly to review the situation and attempt to change mental health laws. There is a possibility that APA may be consulted in the enactment of these changes.

The committee has voiced to the World Psychiatric Association (WPA) its opposition to the *Operational Instrument* designated for use by the WPA Committee to Review Alleged Abuses of Psychiatry. The committee believes that if left as presently written, the *Operational Instrument* will seriously hinder the work and effectiveness of the review committee.

The *Committee on International Abuse of Psychiatry and Psychiatrists* has made a videotape on psychiatric abuse issues that will be shown at the 1987 APA annual meeting. Copies of this videotape can be borrowed from the APA Office of International Affairs.

The *Committee on Human Rights,* Lawrence Hartmann, M.D., chairperson, has expanded its network of contacts and has become increasingly involved in the study of human rights violations around the world. APA cosponsored a mission to Chile in November–December 1985 with the American Psychological Association and the American Committee on Human Rights. The mission was funded by the MacArthur Foundation and was undertaken to investigate the psychological effects of the Chilean government's use of torture on the general population of Chile, the role of psychiatrists and psychologists in torture, and the treatment of torture victims. Dr. Hartmann and the director of the Office of International Affairs participated in this mission, during which they interviewed individuals working for human rights organizations, the leadership of the Medical Association of Chile, psychiatrists and psychologists who work with victims of torture, and the victims themselves. A report on the mission and a personal report of the APA participants have been written and shared with the APA leadership and others. At no expense to itself, APA also cosponsored a follow-up mission in August 1986, after the president and secretary of the Medical Association of Chile were arrested. One of the main charges of that association is the investigation of physicians' roles in torture.

The committee is organizing a symposium to be held at the 1987 APA annual meeting on the psychiatric aspects of torture, using Chile as an example. A psychiatrist from Chile who is knowledgeable about the situation there will participate in this symposium.

The Office of International Affairs has been working with a student intern from the University of Maryland who is writing a report on psychiatry and human rights from the international perspective. The committee has offered suggestions and counsel for this report.

The committee has discussed a number of other subjects, such as guidelines for psychiatrists examining potential defectors, and has facilitated referral to other APA components. The committee continues to monitor the situation in South Africa and advises the APA leadership on when appropriate statements should be made regarding APA's opposition to apartheid in that country.

The *Task Force on Psychological Aspects of the Middle East Peace Process,* George Tarjan, M.D., chairperson, has focused the next phase of its project on the role of education in the peace process. The steering committee for this project, consisting of Egyptians, Israelis, and Palestinians in addition to the task force, has decided that the next phase will examine ways to influence the younger generation in the Middle East through education and the media. Institutions in Egypt, Israel, and Jordan have indicated willingness to participate in this project, which will not proceed until additional outside funding is obtained.

The *InterAmerican Council of Psychiatric Associations,* Evaristo Gomez, M.D., APA delegate, voted to change its statutes and bylaws to broaden the membership to include all eligible psychiatric organizations in the Americas and within the Caribbean Basin. It is anticipated that this will make the council much more viable and active than it has been. New officers have been elected, and membership recruitment has begun. It is hoped that the InterAmerican Council can lead the way for ongoing communication and collaboration between the Americas and the Caribbean Basin.

The *Committee on International Education,* Normund Wong, M.D., chairperson, has now been appointed and is beginning to set up a program whereby postresidency fellowships will be available for psychiatrists who have been fully trained in their countries of origin and will come to the United States for 6 months to 3 years for specialized training. Great emphasis is placed on the fact that assurances must be given that these individuals will return to their home countries on completion of training. In addition, the committee would like to facilitate residency electives whereby U.S. psychiatric residents would spend 3–6 months in other countries for specialized training. The intent of this committee is to screen applicants from other countries, ascertain which departments of psychiatry will be able to offer such fellowships, and offer guidelines for this program. The APA Board of Trustees has authorized a 3-year pilot project, after which recommendations for future work will be made. It is anticipated that during this first 3 years the applicants will be required to provide all of their own funding for this training. It is hoped that if the project is successful, outside funding can be obtained for individuals who cannot provide their own.

The *Task Force to Plan the World Psychiatric Association Regional Symposium,* Robert Hales, M.D., chairperson, has begun its work for this meeting, scheduled for Oct. 13–16, 1988, in Washington, D.C. The theme of the symposium will be "Psychiatric Disorders: Research and Clinical Interface." The morning plenary sessions will focus on affective and anxiety disorders, schizophrenic and organic disorders, and personality and other disorders. The afternoons will feature WPA section symposia, new research poster sessions, workshops, and free papers. Preliminary information regarding the symposium can be obtained from the Office of International Affairs.

The *Task Force to Plan the Joint Meeting in China,* Herbert Pardes, M.D., chairperson, is beginning its work for this meeting, which will be held in 1988. The task force is communicating with the Chinese Medical Association regarding the most appropriate time and location for this meeting and with our colleagues in the People's Republic of China regarding topics of mutual interest. The Office of International Affairs and the Office of Meetings Management will organize a travel package for participants.

The Council on Medical Education and Career Development

Jeffrey L. Houpt, M.D., Chairperson

The council serves APA members by providing recommendations to the APA joint Reference Committee regarding issues that affect psychiatric education for medical students, residents in psychiatry, and other physicians and the career development of psychiatrists. Sixteen committees and task forces raise issues for council consideration and possible referral to the joint Reference Committee, the Assembly, and the Board of Trustees. The committees and task forces also respond to issues that these groups and the council generate. Any APA member can, through the Assembly or the committees and task forces, direct the council's attention to an important policy issue related to psychiatric education and career development. The council includes in its standing membership an Assembly liaison appointed by the Speaker-Elect of the Assembly and President-Elect.

Former President Carol Nadelson, M.D., convened the presidential conference "The Future of Psychiatric Education," which was held in Raleigh, N.C., during April 1986. This conference covered a wide range of issues related to the quality of psychiatric education, its future directions, obstacles to education, and the identification of trends important to the field. The council reviewed the findings from that conference and outlined nine issues on which it would initiate some action.

1. *Entry or transition into the specialty.* For the last 2 years the council has been working with officers of the American Association of Chairmen of Departments of Psychiatry and the American Association of Directors of Psychiatric Residency Training to determine if the national residency matching program can be improved. This ad hoc group has concluded that the match needs to be improved and that its goals might best be accomplished by holding simultaneous matches for postgraduate years 1 and 2. This group is now reporting back to its constituencies to determine what level of support exists and to see if free-standing programs in psychiatry might be interested in collaborating on a uniform match date. The ad hoc group also felt that the time between when a resident sends in a list and the actual match date should be shortened. The National Residency Matching Program agrees that this can be done.

2. *Development of academic psychiatrists.* In some institutions the number of midlevel faculty is declining. Younger faculty are being used for service obligations and are moving into private practice when they are unable to obtain tenure. The council felt that an intersociety consortium of groups concerned with the development of academic psychiatrists should examine this issue.

3. *Development of an intersociety consortium.* The council felt that since the following groups all share an interest in education, a standing consortium of representatives from each of them would be useful for addressing common concerns: Society of Professors of Child Psychiatry, National Institute of Mental Health, American Board of Psychiatry and Neurology, American Academy of Child Psychiatry, American College of Psychiatrists, Association for Academic Psychiatry, American Association of Chairmen of Departments of Psychiatry, American Association of Directors of Psychiatric Residency Training, Association of Directors of Medical Student Education Programs, and Association of American Medical Colleges.

4. *New technology and psychiatric training.* The council asked the Committee on Independent Study to consider how new technologies might be used to improve psychiatric education.

5. *Impact of new forms of practice on psychiatric education.* The council recognized that psychiatry is being practiced in settings different from traditional ones and asked the Committee on Graduate Education and the Committee of Residents to review this issue and report back to the council.

6. *Development of model postgraduate institutes.* The council felt that some thought should be given to the development of postgraduate institutes which can provide additional training for psychiatrists. There is evidence that traditional continuing education courses are limited, and the council asked the Committee on Continuing Education to consider this issue.

7. *Subspecialization.* Whether or not APA formally embraces subspecialization is important for the future of the field. The council has encouraged APA to provide a wide hearing of the issues and to examine the implications of subspecialization for the entire field. It also recommends that "grandfathering" and protection for present members also be considered.

8. *Training of nonpsychiatrist mental health professionals.* The council is preparing a questionnaire to determine the degree to which psychiatry departments participate in the training of nonpsychiatrist mental health professionals.

9. *Funding of psychiatric services.* The council believes that funding for postgraduate positions, particularly in years spent treating outpatients, will increase in importance. Related to such funding is third-party payment for psychotherapy services provided by residents in outpatient settings. The council requested that the Committee on Graduate Education confer with members of the American Association of Directors of Psychiatric Residency Training to collect background information on these issues and report back to the council.

In addition to these concerns, the components of the council have had an active year. The highlights of these committees and task forces follow.

The *Committee on Administrative Psychiatry*, Stuart L. Keill, M.D., chairperson, continues to administer the examination for certification in administrative psychiatry. In May 1986, 19 people took the examination; 10 passed, three failed, and six conditioned.

The *Committee on Medical Student Education*, Gerald A. Melchiode, M.D., chairperson, maintains information booths at the annual meetings of the American Medical Student Association and the Student National Medical Association. This committee is developing an audiovisual tape to address career issues in psychiatry; in the interim it has updated its present exhibit with still-life photographs of psychiatrists in different practice settings. This committee also continues to work on a brochure dealing with the psychiatry resident as teacher. It reported that there are presently 487 Medical Student members in APA.

The *Committee on Graduate Education*, Stefan Stein, M.D., chairperson, diligently assisted the council in its work with the American Association of Directors of Psychiatric Residency Training and the American Association of Chairmen of Departments of Psychiatry to develop recommendations for a simplified and fairer match process. This recommendation was detailed earlier in the report. This group also reviewed the new *Essentials for Child Psychiatry*, and on the basis of the group's recommendation for approval, the Board of Trustees returned them to the Residency Review Committee for implementation.

The *Committee on Continuing Education*, John W. Goethe, M.D., chairperson, has surveyed the district branches on their continuing medical education (CME) activities to determine how the committee might be useful to the district branches. Forty-five district branches have responded, and the report is forthcoming. This committee, in cooperation with the Association for Academic Psychiatry, has completed the regional videotape library network. The United States is divided into 10 regions, and each region has a representative who possesses the tapes. Interested people can get them from the regional representative. Any questions about using the tapes should be directed to the Office of Education, which will determine the appropriate regional representative. This committee is also looking into the feasibility of developing a statement concerning model postgraduate institutes.

The *Committee on Consultation-Liaison Psychiatry and Primary Care Education*, Donald S. Kornfeld, M.D., chairperson, has been

working on defining appropriate liaison with other medical groups and on defining the relationship of these liaisons to APA. It recognizes the need for increased liaison activities and has submitted these recommendations to the Ad Hoc Committee on Liaison Activities. The Committee on Consultation-Liaison Psychiatry and Primary Care Education reported that 1) the American Academy of Family Practice is now developing subspecialty areas in substance abuse and geriatric psychiatry, 2) the results from the Society of Teachers of Family Medicine survey reflect an underutilization of psychiatrists in teaching programs where specific medical competence is required, 3) the American Hospital Association is shifting its general hospital psychiatry representation from inpatient units in general hospitals to for-profit free-standing psychiatric hospitals, and 4) the American College of Obstetricians and Gynecologists Committee on Residency Training in Obstetrics and Gynecology has a psychiatric requirement in its curriculum and is thinking of expanding that requirement.

The *Committee on the Impaired Physician*, Stephen C. Scheiber, M.D., chairperson, has surveyed the district branches and found that only seven of the 27 surveyed have committees on the impaired physician but that several have psychiatrists who work in liaison with the state medical societies. The committee is preparing a paper on the ethics of dealing with impaired physicians. It is intended to provide district branches with guidelines in dealing with an impaired psychiatrist before the case comes to the APA Ethics Committee, to examine the ethics of referral of an impaired physician, and to discuss referral of an impaired physician who has an ethics problem as well. In addition, the committee is analyzing the data on the 15 psychiatrists who were included in the larger AMA study on physician suicide, and it will report the preliminary data on this group. Finally, the committee is developing a component workshop on education and training stresses and adaptation for the 1987 annual meeting.

The *Committee of Residents*, James Landen, M.D., chairperson, has worked most recently on developing guidelines for election of a Member-in-Training trustee to the Board of Trustees. That proposal is presently under consideration by the Board of Trustees. In addition, the residents supported a stepwise increase in dues over the 10 years after training rather than the present abrupt change. This proposal was approved by the Board of Trustees in 1986. The committee reminds training programs that resident contracts are required by the Residency Review Committee and encourages departments to enforce that requirement. Apparently, several programs do not provide the resident with a contract.

The *Committee on Independent Study*, Ian E. Alger, M.D., chairperson, is developing a catalog of independent study materials offering category I CME credit. The first edition will include listings of audiotapes, videotapes, journals, computer software, and a miscellaneous category for items such as the Psychiatric Knowledge and Skills Self-Assessment Program. The committee plans to add descriptive and evaluative commentary in future additions and to expand the list to include learning materials, resources, and databases not nationally approved for category I CME credit but useful for independent study. In addition, the committee will prepare a report on state of the art technology and new learning methods relevant to psychiatric education and individual learning.

The *APA/Burroughs Wellcome Fellowship Selection and Program Committee*, Walter E. Barton, M.D., chairperson, reported that 11 new appointments were made in May 1986 and 10 fellows are in their second year of fellowship. The fellows have proposed a workshop for the 1987 annual meeting titled "Psychiatric Residency: Conflicts and Challenges."

The *APA/Mead Johnson Fellowship Selection Committee*, Charles J. Rabiner, M.D., chairperson, reported that 15 APA/Mead Johnson Fellows were selected this year from among 52 nominations. They will participate in two Institutes on Hospital & Community Psychiatry and one APA annual meeting during their tenures.

The *Selection/Advisory Committee, Minority Fellowship Program*, Charles Pinderhughes, M.D., chairperson, reported that there are eight fellows and three trainee-consultants under the APA/NIMH Minority Fellowship Program for the academic year 1986–1987. The committee is working on a workshop for the 1987 annual meeting.

The *Steering Committee, Psychiatric Knowledge and Skills Self-Assessment Program VI (PKSAP-VI)*, Gordon D. Strauss, M.D., chairperson, is developing PKSAP-VI. It has been decided that PKSAP-VI will be distributed serially in 3-month intervals.

The *Task Force to Facilitate Communication Between the APA and the ABPN*, Richard I. Shader, M.D., chairperson, has been concerned about the performance of foreign medical graduates on the examination provided by the American Board of Psychiatry and Neurology (ABPN). It will develop a component presentation for the 1987 annual meeting in which foreign medical graduates who are examiners for the Board examinations will provide their observations on how foriegn medical graduates might enhance their performance on the Board examinations. The task force has also encouraged programs and individuals to enhance the language, communication, and test-taking skills of foreign medical graduates by such formal approaches as courses in English as a second language, speed-reading, and working with a local preceptor.

The *Committee on Psychiatrist Leadership in Public Mental Health Programs*, Steven E. Katz, M.D., chairperson, has suggested that APA develop formal liaisons with a variety of advocacy groups. This suggestion has been forwarded to the Ad Hoc Committee on Liaison Activities. At the committee's suggestion, and with the endorsement of the joint Reference Committee and the Board of Trustees, district branches have been encouraged to develop relationships with the National Alliance for the Mentally Ill. This group is developing a paper supporting the notion that each state's director of mental health should be a psychiatrist.

The *Task Force on Cost Effectiveness in Consultation-Liaison Psychiatry*, Frederick Guggenheim, M.D., chairperson, has continued to stimulate research on cost effectiveness in consultation-liaison psychiatry. A preliminary report is due in May 1987.

The Council on National Affairs

Pedro Ruiz, M.D., Chairperson

During the last year, the council has addressed a series of issues of national concern for APA and the profession. In so doing, the council worked closely with the Assembly and other relevant APA components. Further, it provided guidance and leadership for its 11 components. Among all of the national issues addressed by the council, a few merit special mention in this annual report.

During the spring of 1986, the council worked hard on the forthcoming National Conference on Terrorism and Health, which it is cosponsoring with Hahnemann University. This conference will relate to all dimensions of planning for disaster and crisis management, and the participants will try to develop appropriate public policy on these issues. This initiative was approved by the council during the 1986 annual meeting; it was also approved by the joint Reference Committee at its June 1986 meeting and, subsequently, by the Board of Trustees. The conference is planned for March 1987. The Tri-Council on the Psychological Aspects of Nuclear Arms Development also worked hard during 1986 to decide the most appropriate steps for APA to follow in this regard. The other two councils that collaborated on this issue were the Council on Children, Adolescents, and Their Families and the Council on International Affairs. The joint council researched the appropriate literature, reviewed relevant activities in several other professional associations, and analyzed preliminary research findings on this issue. The results of these efforts were presented and discussed during the 1986 fall meeting of the Council on National Affairs, at which time the council voted to recommend at the October 1986 meeting of the joint Reference Committee the formation of a committee to deal with this important matter. The Councils on Children, Adolescents, and Their Families and on International Affairs also approved and supported this action. If approved by the joint Reference Committee and the Board of Trustees, this committee will function under the aegis of the Council on National Affairs and will have strong liaison with the Assembly and other appropriate APA components.

During the 1986 annual meeting and fall components meetings, the council reviewed and discussed the need to create a committee on victimization under the Council on National Affairs. It reviewed past APA activities in this regard, and after extensive consideration, decided to work on a proposal for the development of such a component. This proposal will be reviewed early in 1987. The council also began to discuss, on a preliminary basis, the need for the profession to become involved in assistance during and after a national disaster. As a result of these discussions, the council decided to invite two or three prominent experts in this area to a meeting at the APA Central Office in Washington, D.C., to further explore this issue. This meeting was held on Dec. 11, 1986. The results of this meeting will be discussed during the council meeting in May 1987.

The council also dealt with several issues referred by the joint Reference Committee for the council's input. The first of these concerned a summary of actions taken by the AMA House of Delegates and the AMA's "Proposals for the Health Policy Agenda for the American People." Areas of concern were reviewed, and appropriate recommendations were made to the joint Reference Committee and other relevant APA components. Second, the council reviewed the proposal of the Council on International Affairs for a committee on international education. The council felt that this educational program, to be sponsored by APA, was much needed and thus decided to support the idea.

Third, the council reviewed a pilot meeting for psychiatric residents who are foreign medical graduates, organized by the APA and supported by a grant from McNeil Pharmaceutical. This meeting was designed to help foreign medical graduate psychiatrists and psychiatric residents improve communication with American training programs, board certification bodies, and patients. It was held in San Diego, Calif., on Oct. 25–26, 1986.

Fourth, the council discussed the pros and cons of the current subspecialization trends in psychiatry. In summary, the council felt that this matter is so important to the profession that an ad hoc committee of the Board and Assembly should be appointed to thoroughly review it and to formulate appropriate APA policies. This recommendation will be forwarded to the joint Reference Committee for action.

During its deliberation with the Joint Commission on Public Relations, the council addressed and developed strategies related to 1) the impact on the media and patients of the Gartrell-Herman study on sexual contact between patients and psychiatrists and 2) the impact on the public image of psychiatry of the recent debates on and approval of the *DSM-III* revision (*DSM-III-R*).

In cooperation with the Joint Commission on Government Relations, the council planned appropriate ways of dealing with 1) the relationship of the recent U.S. Justice Department ruling on AIDS to persons suffering from AIDS, 2) the recent AMA resolution on antibody testing for AIDS, 3) the recent Supreme Court decision on sodomy, and 4) the Parental Leave Act, particularly insofar as APA is concerned.

Besides the activities already described, the council also worked closely with its 11 components on formulating policies and plans for action on key national issues. A summary of these activities follows.

The *Committee on Religion and Psychiatry*, Marc Galanter, M.D., chairperson, has continued to work on the monograph on religious cults. Articles have already been prepared and are currently being edited. The 1986 Oskar Pfister Award Lecture given by Dr. Hans Küng during the annual meeting was a success. The recipient of the 1987 award will be Dr. Robert Jay Lifton. The topic of Dr. Lifton's lecture will be Nazi doctors. The committee is also planning to hold a workshop during the 1987 annual meeting on the psychology of genocide. In addition, explorations are under way to see if Bishop Desmond Tutu could deliver the 1988 Oskar Pfister Award Lecture. Finally, this committee has started to look into Christian psychiatry and conflicts that have arisen between Christian psychiatrists and mainstream psychiatrists.

The *Committee on Gay, Lesbian, and Bisexual Issues*, James P. Krajeski, M.D., chairperson, continues to advocate elimination of the current discrimination against homosexuals by the military, particularly insofar as confidentiality is concerned. In this regard, collaboration with APA counsel and the APA Committee on Confidentiality is being maintained. Further, efforts to publish educational articles on this matter in *Psychiatric News* are under way. The committee also deliberated on the recent Supreme Court decision about sodomy. Attention was paid to the potential discrimination against gay men and lesbians as a result of this legal decision. Along these lines, this committee will pursue the appropriate dissemination of the 1973 APA position statement on homosexuality and civil rights as a way of minimizing the negative impact of the Supreme Court decision. The committee will also start researching the existence and forms of discrimination against gay and lesbian psychiatric residents and practicing psychiatrists. Further, efforts will be directed toward ending the teaching of homosexuality as pathological, which occurrs in some training programs despite scientific evidence contradicting that view.

The *Task Force on the Psychiatric Aspects of AIDS*, Stuart E. Nichols, Jr., M.D., chairperson, has worked hard since its inception in early 1986. Several scientific presentations organized by this task force were given during the 1986 APA annual meeting. In collaboration with the APA Office of Education, a grant proposal for educational efforts on the psychological aspects of AIDS was submitted to the National Institute on Mental Health (NIMH) last spring. This proposal was approved by NIMH in September 1986, and funding was provided in December 1986. Two position statements were initiated by this task force and approved by the council

during the 1986 fall components meetings. One relates to discrimination based on results of tests for human immunodeficiency virus. The other relates to the acquired immune deficiency syndrome (AIDS), AIDS-related complex, and other related disease states. Both position statements will be submitted to the joint Reference Committee for action. This task force prepared an action item, approved by the council, leading to psychiatric participation at the Third International Conference on AIDS, to be held on June 1–5, 1987, in Washington, D.C. Finally, the task force recommended, and the council concurred, that APA join the AMA's brief submitted to the U.S. Supreme Court opposing the Justice Department's position on AIDS and the Rehabilitation Act.

The *Committee on Women*, Nada Logan Stotland, M.D., chairperson, approved an action item, supported by the council, on *DSM-III-R*. The item recommends to the joint Reference Committee deletion from *DSM-III-R* of the diagnoses of periluteal dysphoric disorder, self-defeating personality disorder, and sadistic personality disorder owing to lack of scientific evidence for their inclusion. Further, this action item also recommends that if the diagnosis of periluteal dysphoric disorder is included in *DSM-III-R*, it should be listed in a clearly demarcated appendix. The committee also continues to work on educating psychiatrists in ethical issues and on the survey regarding sexual contact between patients and psychiatrists. Several scientific publications and educational tapes have resulted from these efforts. Many of these educational tools will be made available to training programs, relevant professional associations, and APA district branches. Scientific presentations are also being planned for the 1987 APA annual meeting. This committee is currently entertaining ideas and proposals for appropriate recognition of the late Dr. Nancy Roeske's contributions to APA and the profession. Organization of a national working conference on the vulnerabilities and strengths of women of different ethnicities is under way. Finally, this committee passed an action item supporting APA's ratification of the United Nations Convention on the Elimination of All Forms of Discrimination Against Women. This action item was approved by the council and is being forwarded to the joint Reference Committee for action.

The *Committee on Occupational Psychiatry*, Duane Q. Hagen, M.D., chairperson, is currently conducting a survey on stress factors in a high-tech environment. This survey, when completed, will lead to a scientific publication. This committee is also developing appropriate liaison with the Center for the Study of Work, which is sponsored by the Institute of Living in Hartford, Conn. In collaboration with the Mobil Oil Corporation, efforts are also under way to study the stress suffered by off-shore oil workers. This collaborative work is aimed at creating innovative approaches to short-term crisis intervention, crisis resolution, and stress reduction training programs. Similar collaborative efforts with the Francek Group were developed with the aim of helping people cope with organizational change, work uncertainty, and work stress. As a result of these activities, appropriate scientific publications and training programs on short-term therapy and employee assistance programs are being planned. Further, this committee is developing a cross-cultural study of employees in the United States and Japan. To this end, committee members visited the Productivity Center in Tokyo, Japan, and the Japan Productivity Center in Arlington, Va. Finally, this committee is considering developing a clearinghouse on psychiatrists' involvement in industry.

The *Committee on Foreign Medical Graduates*, S. Arshad Husain, M.D., chairperson, was able to ensure appropriate APA representation to the AMA Ad Hoc Committee on Foreign Medical Graduate Affairs. As a result of these actions, APA representatives were able to testify during the AMA hearings in January 1986. This committee is currently analyzing the pass/fail rate of foreign medical graduates on the psychiatric board examination. This committee is establishing liaison with the American Board of Psychiatry and Neurology (ABPN) to design measures that could improve the performance of foreign medical graduates on ABPN examinations. This committee is also assisting American Psychiatric Press in the publication of *Manual of Psychiatric Examination*, which is geared toward helping foreign medical graduates become familiar with the ABPN examinations. This committee is also working closely with Assembly representatives to maintain a foreign medical graduate psychiatrist as an observer in the APA Assembly. Finally, this committee is gathering information concerning the foreign medical graduates who are unable to find residency training program positions in this country. It is hoped that this information will lead to ways of ameliorating the situation.

The *Committee of American Indian and Alaskan Native Psychiatrists*, James W. Thompson, M.D., chairperson, is educating members of Congress and strongly advocating reauthorization of the Indian Health Service, the substance abuse bills, and the Native Hawaiian Health Care Act. All of these bills have great impact on the well-being of the Native American populations. This committee has also worked closely with the Association of American Indian Physicians on areas of mutual concern. Several members of the committee attended the 1986 annual meeting of that association and are also involved in the planning and preparation of its 1987 annual meeting. The topic of that meeting will be "destructive behavior among Indian people." These meetings have also been used to provide information and role models for Indian medical students interested in psychiatry. Finally, this committee is working closely with the Indian Health Service in areas of mutual interest, such as that organization's Task Force on Suicide, means for physicians to enter the Indian Health Service, and ways of developing a formal liaison between that group and APA.

The *Committee of Asian-American Psychiatrists*, Joyce S. Kobayashi, M.D., chairperson, is now involved in the final steps of the publication of the *Directory of Asian-American Psychiatrists*. This directory was to be published at the end of 1986. It will undoubtedly help increase the availability of psychiatric services to the Asian-American population and thus greatly improve the quality of psychiatric services for this ethnic minority. This committee is also organizing a reception in conjunction with Prof. B.B. Sethi's International Scholar Lecture during the 1987 APA annual meeting. An official request will be made to the APA Scientific Program Committee for the selection of an Asian-American psychiatrist for one of the yearly International Scholar Lectures delivered during the APA annual meeting. This Asian psychiatrist could address key topics relating to the mental health of Asian-American populations. Finally, the committee is working closely with the Asian Health Forum; work is under way to establish a national data base to facilitate planning and to develop a national resource center.

The *Committee of Hispanic Psychiatrists*, Gladys Egri, M.D., chairperson, is finalizing the Simon Bolivar Lecture for the 1987 annual meeting. The committee is also gathering data on the need for psychiatric care of the Hispanic-American population. This committee is collaborating with the APA Division of Public Affairs on disseminating press releases related to the mental health of Hispanic-Americans to radio and television stations that broadcast in Spanish. It is hoped that these activities will educate Hispanic-Americans and improve the quality of psychiatric services offered to them.

At the request of the APA Assembly and the joint Reference Committee, the *Committee of Black Psychiatrists*, Thelissa A. Harris, M.D., chairperson, reviewed the *Report on Black and Other Minority Health*, issued by the U.S. Department of Health and Human Services (DHHS). As a result of this review, an action item was forwarded to the joint Reference Committee and the APA Board, through the Council on National Affairs. The action item recommends that the APA Medical Director communicate to the DHHS areas of concern regarding this report—for instance, the need for more minority psychiatrists' input in the preparation and publication of reports like this one.

The committee also reviewed the outcome of the conference "Psychiatry in Africa and the Americas Today" held in Nairobi, Kenya, on Aug. 10–14, 1986.

The *Committee on Abuse and Misuse of Psychiatry in the U.S.*, Roger D. Walker, M.D., chairperson, is focusing on ways to minimize the inappropriate admissions of children to psychiatric hospitals. This committee also looked at the increased time demanded of psychiatrists for nonclinical, administrative tasks such as insurance paperwork. These activities might be negatively affecting patient care and could thus constitute an abuse. Finally, this committee is also developing liaison activities with the Council on International Affairs in areas of mutual concern.

The council had heavy agendas at its meetings in May and

September 1986. Council members worked hard to cover these agenda items, and for this the council chairperson expresses his appreciation to the council members: Richard Fields, M.D. (vice-chairperson); David Kessler, M.D.; Lindbergh S. Sata, M.D.; Alexandra Symonds, M.D.; Viola W. Bernard, M.D. (consultant); Amado Suarez, M.D. (observer-consultant); Elissa Benedek, M.D. (Board liaison); Dorothy A. Starr, M.D. (Assembly liaison); Jonathan Sugar, M.D. (APA/Burroughs Wellcome Fellow); Diane Felder, M.D. (APA/NIMH Fellow); and Geraldine Farias-Daniels; M.D. (observer-APA/NIMH Fellow). Further, the council chairperson also thanks the members of all components under the council for their contributions. Finally, the council chairperson is indebted to the APA staff, particularly Ms. Linda Roll, for all the support and invaluable assistance with the council's work.

The Council on Psychiatric Services

Naomi Goldstein, M.D., Chairperson

As stated in the *Operations Manual of the Board of Trustees*, this council concerns itself "with the broad programming aspects of public and private sectors and the delivery of psychiatric services in all types of psychiatric facilities. Those objectives of the association that would promote the treatment of the mentally ill, further the interests of patients, and enhance the qualities of services available are central to the council's work."

Underlying all of the council's work this year, as in recent years, has been the issue of access to psychiatric services for all types of populations and in all types of settings and a concern with the quality of care given. The components of the council have differing focuses and missions, and this difference was reflected in the broad range of actions recommended by the components and taken by the council in the past year.

In addition to specific actions reflecting component activities, the council addressed general issues. First, several years ago APA cosponsored a conference with the National Association of State Mental Health Program Directors and the American Association of Directors of Psychiatric Residency Training. This conference resulted in the paper "Collaboration Between State Mental Health Administrations and Medical School Departments of Psychiatry—A Call to Action." The principal recommendation, supported by the council, was for development of a consortium of academic and state mental health leaders. The document itself and, most particularly, the recommendation for the consortium were endorsed by the council after several revisions by Dr. Frank James, council member, president of the National Association of State Mental Health Program Directors, and former chairperson of the APA Committee on State Hospitals. This effort appears to represent a renewed interest and commitment on the part of the conference participants. The importance of this type of collaboration to administration, education, staffing, and level of care is clear.

The council received a copy of a statement made in Boston by the then president of the National Alliance for the Mentally Ill, Mr. James Howe. Among its many missions, the National Alliance for the Mentally Ill has been attempting to separate mental illness, identified as a physical disease of the brain caused by factors not yet known, from other mental or emotional disturbances that do not have the same type of etiology. That group is concerned with the public's perception that severely mentally ill people are in some way weak, malevolent, or the result of poor parenting and that funds will not be made available for research, treatment, and management. Mr. Howe's statement is a challenge to APA, the council, and other components. In fact, it is important to work closely with the leadership of the advocacy groups. The council agreed to encourage the APA leadership to invite appropriate officials of the National Alliance for the Mentally Ill or other citizen groups to participate prominently in the upcoming annual meetings, and it plans to invite an appropriate leader to join it for the next fall component meetings.

To enhance its understanding of various issues and to facilitate communication among the components, the council met with the Joint Commission on Government Relations and sat with the Council on Economic Affairs.

The council expressed major concern about the plans of the U.S. Department of Defense to accept proposals from competing providers and award three regional contracts for assumption of services and financial risks of care for CHAMPUS beneficiaries. The Division of Government Relations, after collecting input from various components, prepared a letter to be sent by Dr. Melvin Sabshin to the Department of Defense. Pleased with the letter, the council suggested there might be an opportunity to make more specific recommendations for inclusion in the request for proposals and urged the Division of Government Relations to follow up. Issues related to access to care and reimbursement were reviewed in the private sector, particularly within alternative delivery systems.

The council reviewed the AMA health policy agenda without particular recommendations and also reviewed an excellent statement prepared by Onek, Klein, and Farr, "Current Economic Issues in Antitrust." While this was of great interest, there were no specific recommendations. The council noted that the report of the Task Force on Medical Staff By-Laws, concerning privileges and credentials for psychiatrists, had been approved by the Board of Trustees in July. This report is available to the membership.

At the request of the joint Reference Committee and in response to concern expressed in several action papers from the Assembly, the council spent a substantial amount of time trying to develop a plan for a conference tentatively titled "Alternative Delivery Systems: Managed Care in HMOs, PPOs, and Psychiatric Speciality Provider Organizations." The council tentatively recommended that a working conference be held in early 1987 to bring together psychiatrists and other individuals who have experience in providing psychiatric services in alternative delivery systems. They would attempt to identify the issues, make some practical recommendations for the membership and district branches, and, if possible, develop policy recommendations or at least identify areas for policy development by APA itself. The conference would be small and would be held in Washington at APA headquarters. After discussion with the joint Reference Committee, it seemed wise to go back to the Assembly Executive Committee to elicit more of the membership's concerns about holding such a conference and to postpone the conference until the fall of 1987.

The council discussed at length, both with the components and their chairpersons, the issue of subspecialization. This issue has been presented to all of the APA components by their leaders for intense discussion, in part because of concerns of the American Board of Psychiatry and Neurology (ABPN), which has been approached by various subspecialty groups, such as psychiatrists specializing in alcoholism and substance abuse or geriatric psychiatry. These psychiatrists have found themselves competing with other providers, some of whom are certified and may be favored for professional opportunities, possibly to the detriment of patients. The issue is urgent, and the arguments for and against subspecialization are complex; the council, without taking a position, recommended that APA form a work group or task force to collect all relevant information—e.g., data from other medical specialties on the impact of subspecialization on differential reimbursement, training, and research.

The *Committee on Alcoholism*, Richard Frances, M.D., chairperson, presented a statement on chemical aversive conditioning for alcoholism. This is a somewhat controversial treatment that does not include the use of disulfiram and has been used successfully but may pose "greater medical risks than other equally efficacious treatments for alcoholism." The committee recommended that chemical aversive conditioning, e.g., with emetine, lithium, succinylcholine, and apomorphine, should be tried only after documentation that a less risky treatment has failed and there is no medical contraindication or "when other documentation demonstrates reasons for exceptions."

The committee also prepared a statement on subspecialization for the addictions, which it strongly favors while recognizing that every general psychiatrist should have expertise in addictions. The committee supports the development of a special or an added qualification in the addictions by the ABPN after successful completion of the general ABPN examination. It noted that there have been rapid developments in the field and there is now a sufficient body of knowledge for subspecialization and that there are now substantial associations of psychiatrists specializing in alcoholism and addictions, as well as other medical societies focusing on these issues. The committee pointed out that other groups are actively certifying both physicians and other specialists in the field, as a result of which psychiatrists who are not so certified might be excluded from giving care and receiving reimbursement. The council received the statement for forwarding to the joint Reference Committee. The council expressed its concern that psychiatric training programs should be adequate to qualify all general psychiatrists for certification and/or reimbursement in drug abuse, alcoholism, and geriatrics.

Several members of the Committee on Alcoholism are active in the newly formed American Academy for Psychiatrists in Alcoholism and the Addictions. Dr. Frances is president and serves as APA liaison. The committee believes that the membership in general should be made more aware of the issues in substance abuse through activity in the components and the Assembly and that the public should be made aware that psychiatrists are actively involved in the care of substance abusers, as well as patients who are mentally ill.

The *Committee on Drug Abuse*, Edward Kaufman, M.D., chairperson, joined in some of the discussions of the Committee on Alcoholism and believes that subspecialization needs further exploration. The committee prepared the detailed *Position Statement on Psychoactive Substance Use and Dependence: Update on Marijuana and Cocaine*, noting that the most recent position statement on marijuana was adopted in late 1978. The council supported the document, which will be forwarded to the Board of Trustees and Assembly for adoption. In addition, the committee hopes to update the position statement on drugs in schools, which it believes has stood the test of time well, given that it was approved in 1969.

The *Institute on Hospital & Community Psychiatry (H&CP) Program Committee*, William B. Beach, Jr., M.D., chairperson, planned and implemented an excellent program in San Diego. Attendance, over 1,250, was the highest of any H&CP Institute in recent history. Ms. Sandra Hass, coordinator for the Institute, reported that because of concern about anticipated increased costs for the Boston meeting in 1987, the committee sought the council's approval of a modest increase in registration fees for next year. The council approved these changes in fees and passed this recommendation to the joint Reference committee.

The *Committee to Coordinate the Functions of the H&CP Journal, Service, and Institute*, H. Richard Lamb, M.D., chairperson, presented a complex request to the council for reorganization of this component. The H&CP Institute program committee has its own functions, planning and implementing the annual Institute. Coordination between the Institute and the *Journal* and Service is carried on by staff and relevant members. There is a need for greater coordination between the *Journal* and Service. Dr. Lamb and Dr. John Talbott, editor of the *Journal*, noted the dependence of the *Journal* on the H&CP Service, a subscription organization that includes among its benefits the *Journal* itself. The proposed structure was very complicated; advantages and disadvantages of the proposed reorganization were noted, and the proposal will be subject to further discussion.

The *Committee on Rehabilitation*, Arthur Meyerson, M.D., chairperson, has been particularly concerned with the policy of the Health Care Financing Administration (HCFA), which has resulted in denials of Medicare payments for partial hospitalization on the grounds of "inappropriateness of care provided" or "that the care is designed to maintain the patient rather than to bring about active improvement in a reasonable period of time." Dr. Meyerson, Division of Government Relations staff, representatives of the American Association for Partial Hospitalization, and the American Hospital Association have met with HCFA staff to address these issues. In addition, Dr. Melvin Sabshin has written to HCFA; his letter also was endorsed by the National Alliance for the Mentally Ill and the National Mental Health Association. The Committee and Division of Government Relations staff have also met with Congressional leaders to explore Medicare initiatives in day treatment, and Dr. Beatrice Braun of the Task Force on Social Security Income/Social Security Disability Insurance is planning to develop guidelines for partial hospitalization treatment. The committee continues to be concerned about the APA/Social Security Administration project, which has undergone some changes demanded by the Social Security Adminstration that may have an unfavorable result from APA's point of view.

Through Dr. Meyerson, APA has had input to the President's Committee on Employment of the Handicapped. There is concern that the subcommittee on mental illness may be phased out; with the council's agreement. Dr. Sabshin was asked to send a letter to the executive director of the President's Committee on Employment of the Handicapped encouraging it to safeguard the interests of the mentally ill by preserving the subcommittee.

The committee is beginning to explore the development of a formal liaison with the discipline of physical medicine and rehabilitation. With the council's consent, the committee also will draft an appropriate letter to Social Security Administration officials urging support for a major project on disability at UCLA. The committee also reported on the establishment of the van Ameringen Award, which provides a $5,000 honorarium to an individual or institution that has made an outstanding contribution in the field of psychiatric rehabilitation. Nominations for suitable recipients were sought.

The *Committee on Private Practice*, James Margolis, M.D., chairperson, studied the APA governance last year through an informal survey and learned that approximately one-third of the members of APA components earned over 50% of their incomes as nonsalaried psychiatrists in traditional, direct fee-for-service practice. Within the Assembly the proportion is about one-half, which is comparable to the percentage of private practitioners in the membership. The figure of the Assembly was about the same in 1979, but there seems to have been a slight increase in the percentage of private practitioners among component members since then. This is not sufficient, however, and the committee urged that additional private practitioners be appointed to appropriate components.

The committee reported that various problems have arisen since Medicare adopted the use of the *Physicians' Current Procedural Terminology*, 4th edition, several years ago. The committee supports the coding system itself but noted that some practitioners may not use it properly and that fiscal intermediaries do not use a standard interpretation of the codes, resulting in considerable confusion and, in some cases, unwarranted discrimination. The committee urged the council to support its request that APA work with the AMA to encourage HCFA to consider development of a consistent interpretation of the codes by its fiscal intermediaries.

For the 1987 annual meeting the committee is planning a continuing education course on contract negotiations and a component workshop on minorities and private practice.

The *Committee on the Chronically Mentally Ill*, David Cutler, M.D., chairperson, reviewed a number of areas of concern and attempted to prioritize them. Its top priorities for the coming year will relate to the homeless mentally ill, specifically, ways to implement the recommendations of the APA Task Force on the Homeless Mentally Ill, motivate psychiatrists to treat chronic patients, and influence training programs and publications to focus more on this population. It proposed a workshop on voluntary treatment for the homeless mentally ill for the 1987 annual meeting.

The committee met with the Committee on State Mental Health Systems to discuss bed shortages and to look at creative alternatives

for housing, and these committees, together with the Committee on Rehabilitation, further explored areas of mutual concern. In particular, they focused on a national project for the homeless mentally ill sponsored by the Robert Wood Johnson Foundation.

A representative of the National Alliance for the Mentally Ill has been appointed as consultant to the Committee on the Chronically Mentally Ill. With this representative the committee explored the possibility of developing workshops, training sessions, etc., for various professional and lay groups. This committee is vital to the development of positions on the care of a large patient population, and the council was particularly pleased with its renewed activity and with the excellent and thorough discussion of the issues the committee is charged to address.

The *Committee on Psychiatric Services in the Military*, Leonora Petty, M.D., chairperson, reported that it had sponsored a meeting of psychiatrists interested in developing an APA district branch for military psychiatrists. There are approximately 500 military psychiatrists; as of several years ago, only about 40% were members. Military psychiatrists are relocated frequently and have limited opportunities to become involved in district branches, reach leadership positions, or be elected to the Assembly. Working with other suitable APA components, the committee is studying the benefits and the many ramifications of such a district branch, which may eventually lead to a very complicated recommendation without precedent in APA. The council encouraged the committee to explore various options and asked to be kept informed.

There is particular concern about graduate medical education for military psychiatrists, the loss of experienced teachers from military training programs to the private sector, and the importance and need for high-quality general training.

The committee reported that the Henry M. Jackson Foundation for the Advancement of Military Medicine, established to stimulate the science, practice, and professionalism of military medicine, has developed a fund in the name of Bartholomew Hogan. The committee hoped to call its annual workshop the Bartholomew W. Hogan Memorial Workshop and sought advice from the council, which suggested contact with the APA Scientific Program Committee.

The committee also urged continuing APA input to the Department of Defense on the reorganization of CHAMPUS. The committee stressed that it was important that the Secretary of Defense had been made aware of APA's concerns (see sixth paragraph of this report).

The *Committee on Federal Government Health Services*, William Hunter, M.D., chairperson, spent considerable time discussing its role and the needs of its constituencies. The committee expressed its concern that in general and within APA there is fragmentation of various public services—for example, the military, Indian Health Service, and prison systems. It noted that most of the patient populations served by the federal system deal with "entitlements" but that, as applied to these populations, this term might also be interpreted as "imposed rights." The committee discussed whether within APA there might be a caucus of public sector providers that could focus on the patient's perspectives, and it hopes to convene a meeting of other APA components which represent public sector programs. This meeting would be cosponsored by the Committee on Psychiatric Service in the Military.

The *Committee on State Mental Health Systems*, Ernest Klatte, M.D., chairperson, also spent considerable time studying its extended charge, noting the change from a focus on state hospitals to state systems. The committee met with a representative of the National Alliance for the Mentally Ill, the executive director of the National Association of State Mental Health Program Directors, and Dr. E. Fuller Torrey, who recently coauthored a report on state systems. The committee noted that the district branches have been encouraged to work with local chapters of the National Alliance for the Mentally Ill and recommended that the district branches consider establishing a policy of periodically recognizing an individual working within or on behalf of the public system. At the fall component meetings, the committee discussed problems with the National Alliance for the Mentally Ill representative in detail. Subsequently, Dr. Klatte and Dr. David Cutler, chairperson of the Committee on the Chronically Mentally Ill, met with the president of the National Alliance for the Mentally Ill, Mr. Don Richardson, for further discussion of the issues. Through the National Alliance for the Mentally Ill there is input into government policy development, and it is hoped that positions reflecting mutual concerns can be developed.

The committee was encouraged to study a new model commitment law prepared by the National Center for State Courts. The committee hopes to sponsor a component workshop at the 1987 annual meeting that will identify problem areas in the state mental health systems and develop recommendations.

The *Committee on the Practice of Psychotherapy*, Marcia Goin, M.D., chairperson, was established by the Board of Trustees last spring and met for the first time last fall. The committee spent considerable time discussing what it should do, attempting to identify research literature helpful to the membership and discussing reimbursement issues with Dr. Steven Sharfstein and educational issues with Dr. Carolyn Robinowitz. The committee is studying reimbursement issues, negative attitudes and myths about psychotherapy, and the reduction of time allotted to teaching psychotherapy in psychiatric residency programs.

The committee is planning to write a booklet or pamphlet, "How Talking Helps," which will be aimed at a nonprofessional audience and focus on psychotherapy rather than on psychiatrists.

Noting the ambivalence about psychotherapy of APA members themselves, as well as the public at large, the committee was preparing a proposal for an annual meeting presentation on the role of psychotherapy in panic disorders.

The *Task Force on Psychiatric Services in Jails and Prisons*, Henry Weinstein, M.D., chairperson, provided the council with an updated draft position statement that will become part of the guidelines for psychiatric services in jails and prisons. The guidelines are organized around what the task force sees as essential and are structured to correspond to the steps in the criminal justice system—arrest, lockup, jail, prison, and discharge. The council encouraged the task force to cite the applicable AMA standards on health care in prisons within the guidelines and to include some statements on appropriate housing for mentally disturbed patients/inmates. Considerable progress has been made in drafting these much-needed guidelines, which the council hopes to receive in early 1987.

The *Task Force on Professional Practice Issues in Organized/Managed Care Settings*, Dr. Haroutun Babigian, M.D., chairperson, held its organizational meeting during the 1986 annual meeting and attempted at the fall component meetings to develop a plan to accomplish its very large and complex charge. The task force agreed to look at practice issues (but not economic issues) in organized/managed care settings and identified the primary care settings it will address: health maintenance organizations, community mental health centers, proprietary hospitals, state hospitals, and Veterans Administration hospitals. Among the areas it will address are medical responsibilities, supervision, standards of care, and ethical considerations. The task force hopes to organize several focused discussions during the 1987 annual meeting, in which members will be invited to participate. It also hopes to set up focused discussion groups featuring invited experts at the annual meeting. The task force also will participate actively in the conference on alternative delivery systems being planned by the council; this will be an important source of information.

The *Committee on Liaison with the American Hospital Association*, currently without a chairperson, reported this year that the Joint Commission on Accreditation of Hospitals (JCAH) is going to focus on accreditation through a survey of outcome data rather than on process data, and for this reason the committee will seek definition of clinical indicators of quality care. Representatives of the National Association of Private Psychiatric Hospitals, APA, and the American Hospital Association psychiatric services section agreed that their respective organizations should be alert to this step by the JCAH and that the efforts of the three organizations toward development of such indicators should be coordinated.

A second item of considerable concern to the liaison committee was a report that the JCAH is now bidding on contracts with Blue Cross and Prudential to conduct external review audits for health maintenance organizations tied to these insurance companies. Noting that the JCAH is a voluntary accrediting agency that sets standards for quality based on advice of professionals and believing

that there is a potential conflict of interest in the JCAH bids to perform commercial reviews, the joint committee of the American Hospital Association and APA asked the two organizations to communicate to the JCAH their belief that it should not enter into agreements with business/industry which may "undermine the neutrality of its primary function of voluntary accreditation." These recommendations were forwarded directly to the joint Reference Committee for further action without an opportunity for discussion by the council.

The council chairperson is awed by the extraordinary energy, commitment, knowledge, wisdom, and sophistication the members of the committees and task forces and their chairpersons, as well as the members of the council, bring to the business of the association on behalf of patients and APA members. In turn, we are all deeply indebted to the support provided by APA staff, principally Ms. Corky Hart, without whom we really could not function.

The chairperson wishes to thank council members Bert Pepper, M.D., vice-chairperson; J.R. Elpers, M.D., who is leaving the council in May and will be deeply missed; J. Frank James, M.D., whom we welcome to the council this year; Frank Rafferty, M.D.; Rena Nora, M.D., observer/consultant; Chester Schmidt, M.D., Board liaison; Gerald Flamm, M.D., Assembly liaison; Seymour Gers, M.D., Assembly liaison; Allison Doupe, M.D., APA/Burroughs Wellcome Fellow; and Anthony Kim, M.D., APA/NIMH Fellow.

The Council on Psychiatry and Law

Loren H. Roth, M.D., M.P.H., Chairperson

The council continues to be active in many arenas in this changing field. Several council projects of many years' duration are coming to fruition.

During the last year the Assembly of District Branches reviewed and critiqued a council report concerning the psychiatrist's so-called "duty to protect": his or her obligation to take steps to protect third parties from any harm that might be caused by patients, including outpatients and former inpatients. Diverse opinions and suggestions concerning this council report were received from the Assembly. These comments were difficult to integrate and synthesize into a concise APA position. In the interim, several states have either passed legislation on the subject or are now considering legislation. In the last year California, Colorado, Kentucky, Louisiana, and Minnesota have passed legislation limiting the psychiatrist's "duty to protect." In response to these statutes (and the council's previous work), the council has now sent to the Assembly a resource document detailing a suggested approach toward legislation in this area, which the council believes will be useful for states that wish to adopt this approach. The approach recommended by the council would limit causes of action against the psychiatrist to those situations where the patient has communicated to the psychiatrist an explicit threat to kill or seriously injure a clearly identified or reasonablly identifiable victim or victims and the patient has the apparent intent and ability to carry out the threats but the psychiatrist has failed to take such reasonable precautions to prevent the threatened harm as would be taken by a reasonably prudent psychiatrist under the same circumstances. The council's resource document specifies several alternative, legally sufficient precautions that psychiatrists might take to contain harm under these circumstances, including communicating the threat to any identified victim or victims, notifying a law enforcement agency, arranging for the patient to be hospitalized voluntarily, or taking legally appropriate steps to initiate proceedings for involuntary hospitalization. Immunity is provided for the psychiatrist who discloses confidential communications under these circumstances. The council views the approach in its resource document as superior to existing state legislation and as maximally protective of psychiatrists and their patients. Assuming successful review of this document by the Assembly, it will then be ready for use by the district branches.

The council has also submitted for Assembly review a proposed model regulation concerning the patient's right to refuse treatment. Many states at present have resolved the problem of the patient's right to refuse by formulating regulations—typically promulgated by the department of mental health—that provide for internal review procedures to decide this matter. The council has critiqued existing regulations and has formulated a recommended approach that is now undergoing APA review. The model regulation includes two alternative methods of addressing treatment refusal. The first alternative permits medication administration for a committed patient, despite the patient's refusal, after review by an independent outside psychiatrist who determines the treatment to be necessary. The second alternative permits medication administration for patients who refuse treatment only if an independent outside psychiatrist finds both that the treatment is necessary and that the patient lacks the capacity to give or withhold informed consent to medication. Both alternatives are included because of the recognition that there are divergent views on the relevancy of adjudicating patient competency in resolving treatment refusals. The model regulation also stipulates and defines an emergency exception to these procedures that permits brief administration of medication to refusing patients for no longer than 48 hours for involuntary patients and 24 hours for voluntary patients. Time limits for reviews are also specified. The proposed model regulation applies only to adults. The council is presently consulting with the Council on Children, Adolescents, and Their Families to formulate a separate position on children and adolescents. After Assembly review, the proposed regulation (with necessary modifications) will be presented for review by APA's joint Reference Committee.

Over the last year, the *Task Force on Involuntary Outpatient Treatment*, David Starrett, M.D., chairperson, concluded its work, formulating a position paper on this subject that includes model statutory provisions relating to outpatient commitment. This work is intended to complement APA's "Guidelines for Legislation on the Psychiatric Hospitalization of Adults." While the present guidelines provide for release to outpatient treatment of hospitalized involuntarily committed patients, such guidelines are brief and do not provide for outpatient civil commitment as a de novo alternative to inpatient treatment. The task force report reviews this subject, available empirical data, and the relevant conceptual and clinical issues. The newly recommended statutory provisions permit commitment to outpatient treatment for up to 180 days if 1) the person is suffering from a severe mental disorder, 2) without treatment the person a) is likely to cause harm to himself or herself or to suffer substantial mental or emotional deterioration or b) is likely to cause harm to others, 3) the person lacks the capacity to make an informed decision concerning the need for treatment, 4) the person has been hospitalized for treatment of severe mental disorder within the previous 2 years and has repeatedly failed to comply with the prescribed course of treatment outside the hospital, 5) an acceptable treatment plan has been prepared that includes specific conditions with which the patient is expected to comply, 6) there is a reasonable prospect that the patient's disorder will respond to the treatment proposed in the treatment plan, and 7) the treatment facility that is to be responsible for the patient's treatment under the commitment order had agreed to accept the patient and has endorsed the treatment plan. The outpatient commitment order constitutes a

continuing authorization for the police, on request of the director of the facility or the physician, to transport the patient to the treatment facility or the physician's office for the purpose of making personal efforts to obtain the patient's voluntary compliance with the requirements of the outpatient commitment order. There are provisions for revocation of the outpatient civil commitment order if the patient fails to comply.

The procedural details of this approach are now under review by the council. It is anticipated that a final report on this subject will be submitted to the joint Reference Committee and the Assembly shortly. Outpatient civil commitment has become one of the most frequently discussed alternatives for ensuring better community treatment of severely mentally ill persons who are difficult to treat and noncompliant.

During the last year, the council had much interaction with the Work Group to Review *DSM-III* and its chairperson, Dr. Robert Spitzer. The council critiqued the newly proposed *DSM-III-R* category of paraphilic coercive disorder and found it troublesome in certain respects. Dr. Roth provided a discussion and critique of this proposed diagnostic category at a special meeting of the work group. The category was eventually deleted from *DSM-III-R*. The council has also recommended a paragraph for *DSM-III-R* to expand the caveat about potential misuse of diagnostic categories. In its recommended statement for the manual the council stresses that "all classifications and criteria appearing in this manual are formulated for clinical purposes, not legal purposes . . . . What constitutes a mental disorder, mental disability or mental disease for legal purposes must be determined by designated legal authorities in light of the social and moral considerations pertinent to the particular context of the decision being made; although clinical and scientific considerations may be relevant to many legal judgments, they should never be regarded as conclusive." The wording of the caveat continues to be revised by the *DSM-III-R* work group.

A subcommittee of the council continues to work on possible recommended revisions of the December 1982 APA statement on the insanity defense. In response to the final report of the Assembly Task Force to Review the Insanity Defense, eight "controversial" portions of that statement are now being reviewed with the aim of possible updating. To date, the subcommittee has agreed that it would be a good idea to retitle the verdict of "not guilty by reason of insanity" as "not criminally responsible." The subcommittee has also agreed that APA should modify its position and no longer recommend nonhospital confinement for untreatable insanity acquittees. Instead, insanity acquittees should be retained under the aegis of state departments of mental health. Each of the other areas of controversy is under review. The subcommittee expects to have a working first draft of recommendations available for review by the council in May 1987. In making this review, the council is attempting to mobilize, wherever possible, relevant empirical data delineating reforms and changes in the insanity defense since the John Hinckley case.

During the last year the council also spent some time discussing "competency to be executed." Last year the council prepared an overview paper on this subject that was used by the APA Commission on Judicial Action in the formulation of an APA amicus brief for the *Ford v. Wainwright* case, decided by the U.S. Supreme Court in June 1986. The Supreme Court held that the Eighth Amendment prohibits states from inflicting the penalty of death on a prisoner who is incompetent for execution and that Florida's procedures for determining the competency of a death row prisoner were not adequate to afford a full and fair hearing on this critical issue. More substantial procedures must be instituted, beyond review by the governor of possibly one-sided psychiatric opinion. In a concurring opinion delineating the standard for incompetency, Justice Powell wrote that execution is forbidden for "those who are unaware of the punishment they are about to suffer and why they are to suffer it." In a footnote, Justice Powell also noted that "if petitioner is cured of his disease, the state is free to execute him." This Supreme Court ruling poses many potential problems for psychiatry. There is uncertainty about whether it is ethical for psychiatrists to participate in death row evaluations of competency and/or to subsequently treat incompetent prisoners to render them competent for execution. After much discussion, the council was unable to agree, on the basis of principle, whether psychiatric participation in the evaluation and treatment of persons sentenced to execution is consistent with ethical standards. This matter will be further debated at the 1987 APA annual meeting. The council will also continue to discuss this subject with APA's Commission on Judicial Action and the Ethics Committee.

During the last year the council continued to discuss "psychic harm," concluding that while this subject is important, there is presently insufficient need for an APA task force on this subject. Views presented by Clifford D. Stromberg, J.D., former consultant to the council on this subject, are summarized in the July 1986 issue of *Psychiatric Times*.

The council also critiqued the report from the NIH/NIMH Consensus Development Conference on ECT, which was published in the Oct. 18, 1985, issue of *JAMA*. The council reviewed its legal implications and identified problems. Along with the concerns of other APA components, these were summarized by President Carol C. Nadelson, M.D., in a letter to the editor that appeared in *JAMA* on April 18, 1986.

The council has also taken the lead in objecting to the so-called "Daes Report," a United Nations report on protection of persons detained on the grounds of mental ill health or disorder. This report, although not yet a final report of the U.N. Commission on Human Rights, is nevertheless now being distributed by the United Nations. Unfortunately, in its attempt to protect patients' rights, the document assumes an extremely antipsychiatry posture, which the council, other APA components, and the World Psychiatric Association believe to be counterproductive and likely to compromise the provision of services for patients. The report, which is long, complex, and uneven, presents its conclusion in 252 numbered paragraphs and subparagraphs and 47 principles. Both the Council on Psychiatry and Law and the Council on International Affairs have criticized this report. APA (through the joint Reference Committee and by review within the Assembly) is now attempting to rewrite this report to provide an amended version to the U.N. Commission on Human Rights. Alfred Freedman, M.D., took the initial lead in helping alert the psychiatric profession to problems in this report.

Over the last year, the Council's *Committee on Confidentiality*, Aron S. Wolf, chairperson, has been active on many fronts. It staffed a booth at the 1986 APA annual meeting that provided a videotaped introduction to confidentiality. Among the issues being discussed by the committee are the need for drafting a model "time-limited consent form" for use by patients in authorizing release of medical information, potential problems associated with CHAMPUS peer review (the need to ensure patient confidentiality to the greatest extent possible under peer review procedures), and the need for military psychiatrists to warn their patients of any potential limitations on patient confidentiality in the military. The committee's most significant effort over the last year, however, has been its formulation of a report titled "Principles of Confidentiality." This report is meant to be a concise, updated statement concerning the importance of confidentiality in psychiatric practice. The report includes guidelines for ensuring confidentiality in a variety of practice settings and with differing patient groups. This statement, although relatively brief, is also comprehensive. A draft of the report is presently available; it is undergoing council review with an aim of submission to the joint Reference Committee and Assembly in 1987.

Over the last year the committee was also successful in influencing the AMA to approve a report urging employers and health insurers to adopt policies and practices preserving the confidentiality of employees' medical information and opposing employment discrimination based on health conditions not related to job requirements or based on use of health benefits. AMA approved this report in June 1986. A useful editorial on the importance of protecting the privacy of employees' medical records appeared in *AMA News* on Oct. 10, 1986.

Over the next year the council hopes to complete the majority of these activities. It will then turn its attention to other matters. In particular, economic and antitrust issues are now coming to the council's attention. The council is also preparing a draft paper that addresses the relationship of medical and legal definitions of mental disorder, particularly as pertains to patient responsibility.

The Council on Research

Herbert Pardes, M.D., Chairperson

Since the establishment of the Office of Research a year ago, the Council on Research has been planning its own reorganization so that it will parallel the office more closely and can streamline, oversee, and integrate its own current functions and tasks. Although in the past the council has mainly established time-limited, task-oriented components to address specific issues of concern to various groups or individuals, the structure being proposed by the council includes standing committees related to the council's three major functions: science policy, scientific assessment, and research. The new structure includes the Committee on Science Policy, the Committee on Diagnosis and Assessment, and the Committee on Research on Psychiatric Treatments. Once the new structure is in place, some assignments previously accomplished by task forces will be subsumed by the committees, and the need for additional task forces will be reduced. These committees will also assume purview over appropriate existing task forces, which will remain until their tasks are completed.

The council has been gratified by the increasingly effective advocacy efforts by APA, the American College of Neuropsychopharmacology, the American Association of Chairmen of Departments of Psychiatry, other medical/scientific organizations, and various citizens groups, which have strengthened the number of research activities supported by the Alcohol, Drug Abuse, and Mental Health Administration and have increased recognition of the field.

In concert with its science policy activities, the council met with leaders of the National Institute of Mental Health (NIMH) and the National Institute on Drug Abuse to review developments and priorities within both institutes. The council was especially interested in institute-level physician involvement in research activities and expressed concern about the number of psychiatrists in initial review groups. The council and APA staff are exploring with NIMH subjects in which there are shortages of qualified psychiatric reviewers in an effort to increase the number of psychiatrists in initial review groups.

The council also met with representatives of various citizens' groups, including the National Alliance for the Mentally Ill, the National Mental Health Association, and the National Depressive and Manic Depressive Association, to exchange information and discuss issues of mutual concern. The council and these representatives agreed on the importance of coordinating the efforts of their organizations to increase advocacy for patients, end the stigma of mental illness, and increase funds for research and treatment and on the need to combine efforts to develop strategies for achieving these goals. The council will continue these exchanges.

Through the efforts of the Office of Research, the council continues to monitor animal research issues, research training issues, research funding sources, and APA research projects. The council agreed that at future meetings it would be useful to limit special focus to three or four major issues. In addition to those just mentioned, topics suggested for focus include experimental drugs, care of the chronically mentally ill, treatment research, and prevention research.

APA remains an important resource for research by individuals and by groups both inside and outside APA. Currently, when a survey or questionnaire is proposed for distribution to any portion of the membership, it must first be reviewed and approved by the Council on Research. The council has in the past expressed some concern about whether reviewing every questionnaire has been an appropriate use of its members' time and expertise. It has proposed a new policy for the *Operations Manual of the Board of Trustees* that would place responsibility for policy concerning such research questionnaires in the council's hands but would assign assessment of the survey instrument, purpose, etc., to the director of the Office of Research and the Department of Manpower, who would routinely report on these activities to the council.

The council continues to monitor APA's Social Security Disability Insurance evaluation study. The project is currently in phase 2 (phase 1 was design of the study). Phase 2, implementation, has two parts: 1) to collect the data and define the scope of work and 2) to identify areas for further study.

The council recommended that the Committee to Evaluate *DSM-III* be disbanded with thanks. The final report and recommendations of this committee were presented a year ago.

In addition to the three standing committees mentioned previously, the council is also recommending the establishment of a task force on prevention research to examine this emerging field, summarize existing information, and identify prevention research opportunities relevant to psychiatry. Outside funding for this component will be sought.

Currently the council has nine components. Highlights of their activities follow.

The *Task Force on Psychosocial Treatment Research*, John Docherty, M.D., chairperson, is outlining its strategy and looking at three main areas: Who is doing research in this field? What is the specific research being carried out? and How is it being funded? To this end, the task force is currently surveying various groups to determine their current levels of research activity, reviewing the psychiatric literature, and initiating liaison with appropriate APA components and others. It hopes to have some recommendations for the council at its spring meeting.

The *Task Force on the Use of Laboratory Tests in Psychiatry*, Alexander Glassman, M.D., chairperson, has completed its report on the dexamethasone suppression test (DST). The council has recommended to the joint Reference Committee and the Board of Trustees publication of the report in the *American Journal of Psychiatry*. Essentially the report states that there is no question that an abnormal DST result is associated with depression. Problems arise, however, when trying to use the test for diagnostic purposes in selected populations, as was originally suggested. However, recent observations have indicated that the test may yet prove useful in predicting treatment response and treatment failure.

The *Task Force to Develop a Safety and Performance Standard for ECT Devices*, Richard Weiner, M.D., chairperson, indicated that the recommendations of the NIH/NIMH Consensus Development Conference on ECT were far-reaching; they called for standards of practice in ECT, means of ensuring compliance with these standards, and a survey of ECT use in this country. The task force feels that the next step should be a joint APA/NIMH meeting to set an agenda for further action. Dr. Weiner will work with Office of Research staff to develop such a meeting.

APA's petition for reclassification of ECT devices is still pending. The task force also will revise its 1982 standard in light of new research and the standard developed by the International Electrotechnical Commission. The task force expects to begin a revision within the year.

The *Task Force on Tardive Dyskinesia*, John Kane, M.D., chairperson, is currently working on a report on tardive dyskinesia. The task force is also considering production of a film or videotape to accompany the report. A detailed proposal of this videotape, including the intended audience, production costs, mode of distribution, etc., was approved by the joint Reference Committee. The task force will seek outside funding for this project.

The *Task Force on Treatments of Psychiatric Disorders*, Toksoz Byram Karasu, M.D., chairperson, has received preliminary drafts of all but two of the 23 chapters that are being developed for its document. These chapters are currently in the process of being reviewed by outside consultants. The remaining two draft chapters are being prepared and should be ready for the council to review at its spring meeting.

The work of this task force has been the subject of extensive

discussion by the Assembly, the joint Reference Committee, and the Board of Trustees. Most agree that it is premature to decide the sort of imprimatur under which the book should be published. All agree that it should not be called a "manual" and should contain clear caveats on the limitations of its recommendations for individual patients.

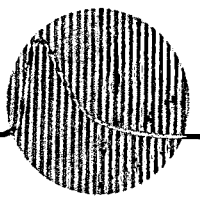
The *Committee on the Biographical Directory and Related Professional Activities Research*, David Knesper, M.D., chairperson, continues its preparations on the 1988 biographical directory and related research activities. The committee has been approached by various groups interested in doing survey research who wish to piggyback their surveys onto the biographical survey, and it has developed a policy on selection of proposed surveys. In addition, the committee will collaborate with the Council on Research on policies for the release of APA data.

The *Task Force on Benzodiazepine Dependency*, Carl Salzman, M.D., chairperson, met in early 1986 to determine the scope and intent of its investigation. Assignments to individual task force members were made, and the task force anticipates that a thorough, state of the art document will be available sometime during 1987 or 1988.

It is anticipated that in 1987 two of the current task forces will have completed their reports and will be disbanded. These are the *Task Force on Sudden Death*, George Simpson, M.D., chairperson, and the *Task Force to Study the Long-Term Effects of Lithium on the Kidney*, George Heninger, M.D., chairperson.

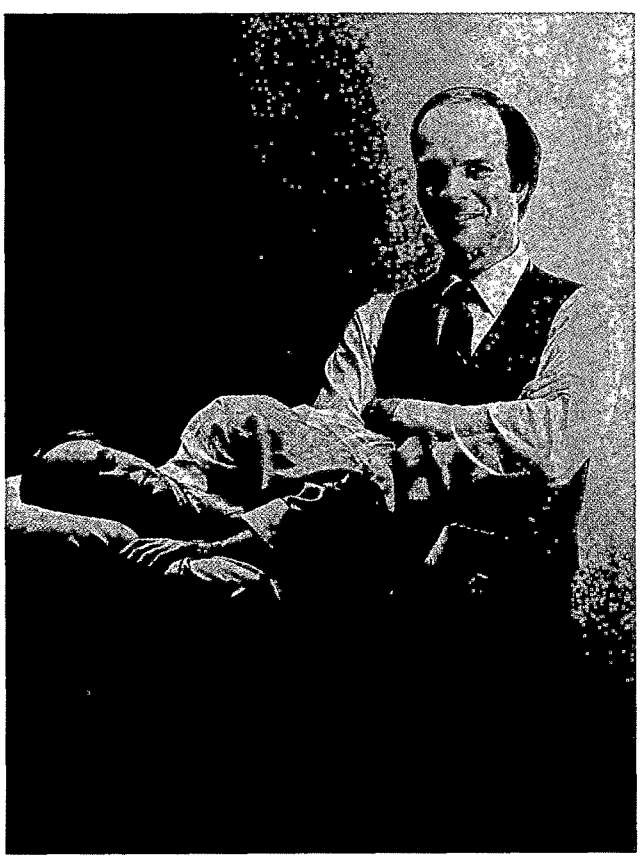
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CONTRAINDICATIONS: Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS: Overdosage may occur at four times the maximum recommended therapeutic dose. Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS: *General:* In elderly and/or debilitated patients, treatment should be initiate at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed ir patients with impaired renal or hepatic function and chronic pulmonary insufficiency. *Information for Patients:* Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing prescribed dosage, (e) possible worsening of sleep after discontinuing HALCION. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported, e.g., coadministration with either cimetidine or erythromycin reduced clearance, prolonged elimination half-life, and approximately doubled plasma levels of triazolam, hence increased clinical observation and consideration of dosage reduction may be appropriate. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. *Pregnancy:* Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. *Nursing Mothers:* Administration to nursing mothers is not recommended. *Pediatric Use:* Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS: During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g., drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE: *Controlled Substance:* HALCION Tablets are a Controlled Substance in Schedule IV. *Abuse and Dependence:* Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE: Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measure when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

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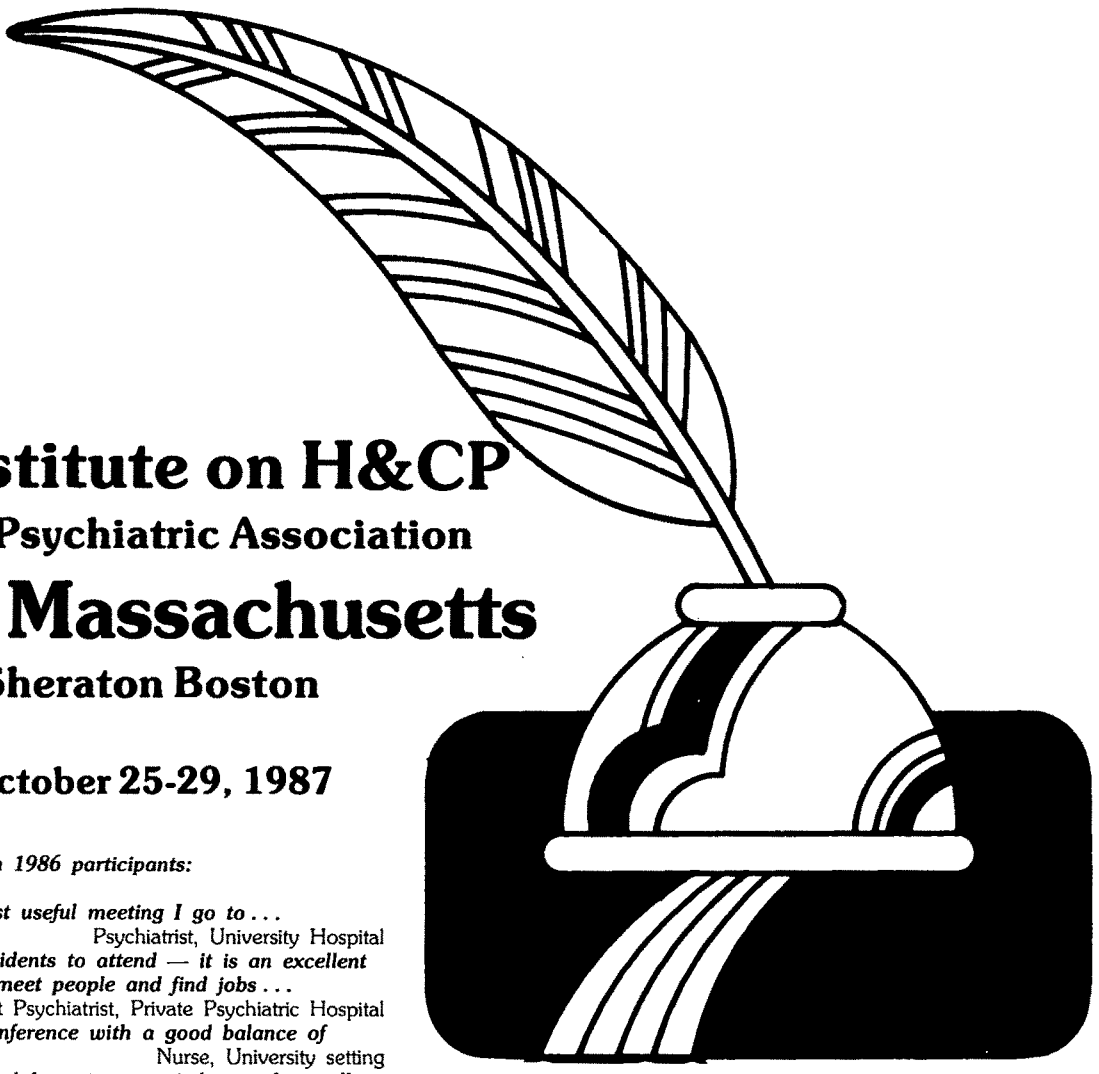
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JUNE

June 3–6, annual meeting, National Council of Community Mental Health Centers, Miami Beach, Fla. Contact Frank H. Bailey, Executive Director, 6101 Montrose Rd., Suite 360, Rockville, MD 20852; 301-984-6200.

June 4–6, annual conference, Society for Menstrual Cycle Research, Ann Arbor, Mich. Contact Nancy Reame, Ph.D., R.N., Program Director, Parent-Child Nursing, University of Michigan, 400 N. Ingalls, Ann Arbor, MI 48109; 313-763-0016.

June 10–12, Tenth International Meeting of the Harry Benjamin International Gender Dysphoria (Transsexualism) Society, Amsterdam. Contact Aaron Billowitz, M.D., Program Chairman, 3395 Scranton Rd., Cleveland, OH 44109; 216-459-4605.

June 11–14, annual meeting, American Association of Neuropathologists, Seattle. Contact James M. Powers, M.D., Executive Director, MUSC Dept. of Pathology, 171 Ashley Ave., Charleston, SC 29452; 803-792-3581.

June 14–18, annual meeting, National League for Nursing, Washington, D.C. Contact Pamela J. Maraldo, Ph.D., R.N., Executive Director, 10 Columbus Circle, New York, NY 10019; 212-582-1022.

June 14–19, 6th International Catecholamine Symposium, Jerusalem. Contact Prof. R. Haim Belmaker, Chairman, P.O. Box 983, Jerusalem, 91009, Israel; 02-527335; Telex 341171 KENS IL.

June 15–19, annual meeting, Committee on Problems of Drug Dependence, Philadelphia. Contact William L. Dewey, Ph.D., Chairman, P.O. Box 613, MCV Station, Richmond, VA 23298; 804-786-8406.

June 18–19, annual meeting, Association of Directors of Medical Student Education in Psychiatry, Denver. Contact Deborah C. Roth, D.O., Dept. of Psychiatry, Box 14, University of South Florida, 12901 N. 30th St. Tampa, FL 33612; 813-974-4242.

June 19–20, annual meeting, National Congress of Parents and Teachers, Dallas. Contact Robert N. Woerner, Executive Administrator, 700 N. Rush St., Chicago, IL 60611; 312-787-0977.

June 21–25, annual meeting, American Medical Association, Chicago. Contact James H. Sammons, M.D., Executive Vice-President, 535 N. Dearborn St., Chicago, IL 60610; 312-645-5000.

June 22–25, annual meeting, British Medical Association, Bristol, United Kingdom. Contact Dr. J.D.J. Harvard, Secretary, BMA House, Tavistock Square, London, WC1M 9JP, United Kingdom; 01-387-4499.

June 26–28, annual meeting, The Huxley Institute for Biosocial Research, Atlanta. Contact Mary E. Haggerty, Executive Director, 900 N. Federal Hwy., Suite 330, Boca Raton, FL 33432; 303-393-6167, 800-847-3802.

June 28–July 3, annual meeting, Sleep Research Society, Copenhagen. Contact J. Christian Gillin, M.D., Executive Secretary, Dept. of Psychiatry, M003, University of California, S.D., La Jolla, CA 92037; 619-452-2137.

June 30–July 2, annual meeting, Royal College of Psychiatrists, Belfast. Contact Dr. Thomas H. Bewley, President, 17 Belgrave Square, London, SW1X 8PG, United Kingdom; 01-235-2351.

JULY

July 19–24, First International Symposium on Management of Pain, Stress, Fear and Anxiety, Tel-Aviv, Israel. Contact Prof. Y. Sharav, Hebrew University-Hadassah, P.O. Box 1172, Jerusalem, 91010, Israel; 972-2-446146.

July 31–August 2, 8th Biennial MRI Conference, Solutions-Pseudosolutions-Ultrasolutions, San Francisco. Contact MRI Conference, 555 Middlefield Rd., Palo Alto, CA 94301; 415-321-3055.

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Contraindications: Known sensitivity to benzodiazepines or acute narrow-angle glaucoma.

Warnings: Not recommended in primary depressive disorders or psychoses. As with all CNS-acting drugs, warn patients not to operate machinery or motor vehicles, and of diminished tolerance for alcohol and other CNS depressants.

Physical and Psychological Dependence: Withdrawal symptoms like those noted with barbiturates and alcohol have occurred following abrupt discontinuance of benzodiazepines (including convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug addicts and alcoholics, should be under careful surveillance when on benzodiazepines because of their predisposition to habituation and dependence. Withdrawal symptoms have also been reported following abrupt discontinuance of benzodiazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility for suicide.

For elderly or debilitated patients, initial daily dosage should not exceed 2mg to avoid oversedation. Terminate dosage gradually since abrupt withdrawal of any antianxiety agent may result in symptoms like those being treated: anxiety, agitation, irritability, tension, insomnia and occasional convulsions. Observe usual precautions with impaired renal or hepatic function. Where gastrointestinal or cardiovascular disorders coexist with anxiety, note that lorazepam has not been shown of significant benefit in treating gastrointestinal or cardiovascular component. Esophageal dilation occurred in rats treated with lorazepam for more than 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times maximum human therapeutic dose of 10mg/day). Effect was reversible only when treatment was withdrawn within 2 months of first observation. Clinical significance is unknown; but use of lorazepam for prolonged periods and in geriatrics requires caution and frequent monitoring for symptoms of upper G.I. disease. Safety and effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukopenia; some have had elevations of LDH. As with other benzodiazepines, periodic blood counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines produce CNS depressant effects when administered with such medications as barbiturates or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic potential emerged in rats during an 18-month study. No studies regarding mutagenesis have been performed.

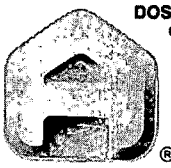
PREGNANCY: Reproductive studies were performed in mice, rats, and 2 strains of rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, malrotated limbs, gastroschisis, malformed skull and microphthalmia) were seen in drug-treated rabbits without relationship to dosage. Although all these anomalies were not present in the concurrent control group, they have been reported to occur randomly in historical controls. At 40mg/kg and higher, there was evidence of fetal resorption and increased fetal loss in rabbits which was not seen at lower doses. Clinical significance of these findings is not known. However, increased risk of congenital malformations associated with use of minor tranquilizers (chlordiazepoxide, diazepam and meprobamate) during first trimester of pregnancy has been suggested in several studies. Because use of these drugs is rarely a matter of urgency, use of lorazepam during this period should almost always be avoided. Possibility that a woman of child-bearing potential may be pregnant at institution of therapy should be considered. Advise patients if they become pregnant to communicate with their physician about desirability of discontinuing the drug. In humans, blood levels from umbilical cord blood indicate placental transfer of lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in human milk like other benzodiazepines. As a general rule, nursing should not be undertaken while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of therapy and generally disappear on continued medication or on decreasing dose. In a sample of about 3,500 anxious patients, most frequent adverse reaction is sedation (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadiness (3.4%). Less frequent are disorientation, depression, nausea, change in appetite, headache, sleep disturbance, agitation, dermatological symptoms, eye function disturbance, various gastrointestinal symptoms and autonomic manifestations. Incidence of sedation and unsteadiness increased with age. Small decreases in blood pressure have been noted but are not clinically significant, probably being related to relief of anxiety.

Transient amnesia or memory impairment has been reported in association with the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind multiple agents may have been taken. Manifestations of overdosage include somnolence, confusion and coma. Induce vomiting and/or undertake gastric lavage followed by general supportive care, monitoring vital signs and close observation. Hypotension, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.



DOSAGE: Individualize for maximum beneficial effects. Increase dose gradually when needed, giving higher evening dose before increasing daytime doses. Anxiety, usually 2-3mg/day given b.i.d. or t.i.d.; dosage may vary from 1 to 10mg/day in divided doses. For elderly or debilitated, initially 1-2mg/day; insomnia due to anxiety or transient situational stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

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Books Received

Alcohol: Our Favourite Drug. New Report on Alcohol and Alcohol-Related Problems From a Special Committee of the Royal College of Psychiatrists. New York, Tavistock (Methuen, distributor), 1986, 206 pp., $45.00; $14.95 (paper).

AIDS in the Mind of America, by Dennis Altman. Garden City, N.Y., Anchor Press (Doubleday & Co.), 1986, 216 pp., $8.95 (paper).

Atlas Clinic de Electroencefalografie, by Prof. Constantin Arseni and Dr. Ignat Roman. Bucharest, Romania, Editura Ştiinţifică Şi Enciclopedică, 1986, 371 pp., no price listed.

Basic Family Therapy, 2nd ed., by Philip Barker, M.D., B.S., F.R.C.P.(Ed), F.R.C.Psych., F.R.C.P.(C), D.P.M., D.C.H. New York, Oxford University Press, 1986, 318 pp., $16.95 (paper).

Clinical Criminology: The Assessment and Treatment of Criminal Behaviour, edited by Mark H. Ben-Aron, Stephen J. Hucker, and Christopher D. Webster. Toronto, University of Toronto, Clarke Institute of Psychiatry, 1985, 311 pp., $17.50 (paper).

Using Manpower Training Programs in the Vocational Rehabilitation of the Mentally Restored: Altro Institute for Rehabilitation Studies Professional Monograph Series, vol. 2, edited by Bertram J. Black. New York, Altro Health and Rehabilitation Services, 1986, 111 pp., $11.50 (paper).

Mother, I Have Something to Tell You, by Jo Brans; research by Margaret Taylor Smith. Garden City, N.Y., Doubleday & Co., 1987, 322 pp., $17.95.

Malpractice: A Guide to Avoidance and Treatment, by Kenneth E. Brooten, Jr., M.A., J.D., and Stu Chapman. Orlando, Fla., Grune & Stratton (Harcourt Brace Jovanovich), 1987, 223 pp., $29.50.

Behavioural Psychotherapy in Primary Care: A Practice Manual, by Tom Carnwath, M.R.C.G.P., M.R.C.Psych., and David Miller, M.A. (Hon.), Dip. Clin. Psych. Orlando, Fla., Academic Press (Harcourt Brace Jovanovich), 1986, 394 pp., $69.95.

Risk Management and Quality Assurance: Issues and Interactions, edited by Greg Chapman-Cliburn. Chicago, Joint Commission on Accreditation of Hospitals, 1986, 152 pp., $30.00 (paper).

A Psychoanalysis of Jesus Christ, by John Chypre. Princeton, N.J., New Wine Press and Peaches 'n' Cream Trust, 1986, 75 pp., no price listed (paper).

Teens Talk About Alcohol and Alcoholism: Written by Students From the Mount Anthony Union Junior High School in Bennington, Vermont, edited by Paul Dolmetsch and Gail Mauricette. Garden City, N.Y., Dolphin Books (Doubleday & Co.), 1987, 119 pp., $12.95; $6.95 (paper).

Healing From the War: Trauma and Transformation After Vietnam (1985), by Arthur Egendorf. Boston, Shambhala (New York, Random House, distributor), 1986, 316 pp., $9.95 (paper).

The Psychotic Core, by Michael Eigen, Ph.D. Northvale, N.J., Jason Aronson, 1986, 380 pp., $30.00.

Language and Speech Disorders in Children, by Jon Eisenson. New York, Pergamon Press, 1986, 130 pp., $19.50; $10.95 (paper).

Adolescent Anger Control: Cognitive-Behavioral Techniques, by Eva L. Feindler and Randolph B. Ecton. New York, Pergamon Press, 1986, 151 pp., $19.50; $10.95 (paper).

Disorders of Eating Behaviour: A Psychoneuroendocrine Approach, edited by E. Ferrari and F. Brambilla. New York, Pergamon Press, 1986, 401 pp., $85.00.

Culture Shock: Psychological Reactions to Unfamiliar Environments, by Adrian Furnham and Stephen Bochner. New York, Methuen, 1986, 284 pp., $45.00; $14.95 (paper).

Institutions Observed: Towards a New Concept of Secure Provision in Mental Health, by Larry Gostin. London, King Edward's Hospital Fund for London (New York, Oxford University Press, distributor), 1986, 172 pp., $13.95 (paper).

Content Analysis of Verbal Behavior: Significance in Clinical Medicine and Psychiatry, edited by L.A. Gottschalk, F. Lolas, and L.L. Viney. New York, Springer-Verlag, 1986, 267 pp., $42.50 (paper).

Panic and Phobias: Empirical Evidence of Theoretical Models and Longterm Effects of Behavioral Treatments, edited by I. Hand and H.-U. Wittchen. New York, Springer-Verlag, 1986, 127 pp., $25.00.

From Learning to Love: The Selected Papers of H.F. Harlow, edited by Clara Mears Harlow. New York, Praeger, 1986, 334 pp., $55.00.

Psychosocial Interventions With Sensorially Disabled Persons, edited by Bruce W. Heller, Ph.D., Louis M. Flohr, M.D., and Leonard S. Zegans, M.D. Orlando, Fla., Grune & Stratton (Harcourt Brace Jovanovich), 1987, 259 pp., $39.50.

New Results in Depression Research, edited by H. Hippius, G.L. Klerman, and N. Matussek, with the assistance of M. Schmauss. New York, Springer-Verlag, 1986, 260 pp., $42.90 (paper).

The Creative Imperative: A Four-Dimensional Theory of Human Growth and Planetary Evolution, by Charles M. Johnston, M.D. Berkeley, Calif., Celestial Arts, 1986, 401 pp., $14.95 (paper).

Somatization and Hypochondriasis, by Robert Kellner. New York, Praeger, 1986, 388 pp., $60.00.

Understanding and Treating Attention Deficit Disorder, by Edward A. Kirby and Liam K. Grimley. New York, Pergamon Press, 1986, 126 pp., $19.50; $10.95 (paper).

On Being a Therapist, by Jeffrey A. Kottler. San Francisco, Jossey-Bass, 1986, 163 pp., $19.95.

The Kiss of the Snow Queen: Hans Christian Andersen and Man's Redemption by Woman, by Wolfgang Lederer. Berkeley, University of California Press, 1986, 253 pp., $22.50.

Progress in Experimental Personality Research, vol. 14, edited by Brendan A. Maher and Winifred B. Maher. Orlando, Fla., Academic Press (Harcourt Brace Jovanovich), 1986, 267 pp., $55.00.

Incest and Sexuality: A Guide to Understanding and Healing, by Wendy Maltz and Beverly Holman. Lexington, Mass., Lexington Books (D.C. Heath & Co.), 1987, 162 pp., $22.00.

Therapeutic Discourse and Socratic Dialogue, by Tullio Maranhão. Madison, University of Wisconsin Press, 1986, 272 pp., $22.50.

What to Do About AIDS: Physicians and Mental Health Professionals Discuss the Issues, edited by Leon McKusick. Berkeley, University of California Press, 1986, 197 pp., $20.00; $8.95 (paper).

Radiation Therapy Simulation Workbook, by Sue Mizer, R.T.(T.), Rhonda Rodgers Scheller, R.T.(T.), and James A. Deye, Ph.D. New York, Pergamon Press, 1986, 170 pp., $50.00 (looseleaf binder).

L'Anxiété, edited by P. Pichot. Paris, Masson, 1986, 207 pp., 225 French francs (paper).

Dreams: A Key to Self-Knowledge, by Zygmunt A. Piotrowski, Ph.D., with Albert M. Biele, M.D. Hillsdale, N.J., Lawrence Erlbaum Associates, 1986, 179 pp., $24.95.

Split Minds/Split Brains: Historical and Current Perspectives, edited by Jacques M. Quen, M.D. New York, New York University Press (Columbia University Press, distributor), 1986, 177 pp., $38.00.

Counseling Exceptional Students, edited by Anthony F. Rotatori, Ph.D., Paul J. Gerber, Ph.D., Freddie W. Litton, Ed.D., and Robert A. Fox, Ph.D. New York, Human Sciences Press, 1986, 314 pp., no price listed (paper).

Dimensions of Grief: Adjusting to the Death of a Spouse, by Stephen R. Schuchter. San Francisco, Jossey-Bass, 1986, 350 pp., $24.95.

Cognition and Affect: A Developmental Psychology of the Individual, by Laurence R. Simon, Ph.D. Buffalo, N.Y., Prometheus Books, 1986, 276 pp., $19.95.

Infant Depression: Paradigms and Paradoxes, by Paul V. Trad. New York, Springer-Verlag, 1986, 329 pp., $45.00.

Career Women and Childbearing: A Psychological Analysis of the Decision Process, by Carole A. Wilk. New York, Van Nostrand Reinhold, 1986, 297 pp., $29.95.

Fifth International Sakharov Hearing Proceedings, April, 1985, edited by Allan Wynn, Martin Dewhirst, and Harold Stone. London, Andre Deutsch, 1986, 210 pp., £5.95 (paper).

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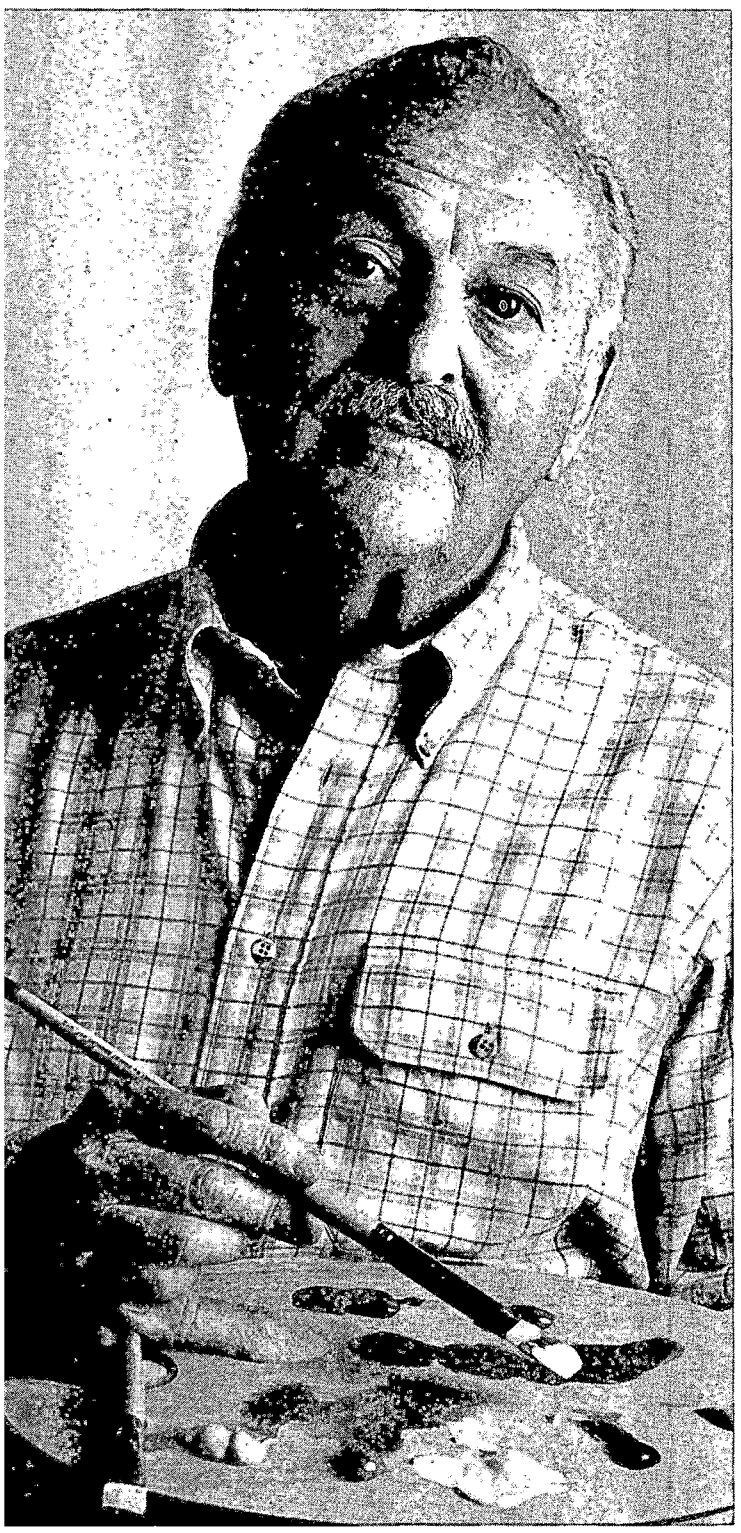
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Usage in Pregnancy: Studies in pregnant patients have not been carried out. Animal reproductive studies have not demonstrated a teratogenic potential. Anticipated benefits must be weighed against the unknown risks to the fetus if used in pregnant patients.

Nursing Mothers: Data are not available on the content of MOBAN in the milk of nursing mothers.

Usage in Children: Use of MOBAN in children below the age of twelve years is not recommended because safe and effective conditions for its usage have not been established. MOBAN has not been shown effective in the management of behavioral complications in patients with mental retardation.

Sulfites Sensitivity: MOBAN Concentrate contains sodium metabisulfite, a sulfite that may cause allergic-type reactions (e.g. hives, itching, wheezing, anaphylaxis) in certain susceptible persons. Although the overall prevalence of sulfite sensitivity in the general population is probably low, it is seen more frequently in asthmatics or in atopic nonasthmatic persons.

PRECAUTIONS: Some patients may note drowsiness initially; advise against activities requiring mental alertness until response to the drug has been established. Increased activity has been noted in patients receiving MOBAN. Caution should be exercised where increased activity may be harmful. MOBAN does not lower the seizure threshold in experimental animals to the degree noted with more sedating antipsychotic drugs; in humans convulsive seizures have been reported in a few instances. This tablet preparation contains calcium sulfate as an excipient; calcium ions may interfere with the absorption of preparations containing phenytoin sodium and tetracyclines. MOBAN has an antiemetic effect in animals. A similar effect may occur in humans and may obscure signs of intestinal obstruction or brain tumor. Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

ADVERSE REACTIONS: CNS EFFECTS: Most frequently occurring effect is initial drowsiness that generally subsides with continued usage or lowering of the dose. Noted less frequently were depression, hyperactivity and euphoria.

Neurological—Extrapyramidal Reactions noted below may occur in susceptible individuals; usually reversible with appropriate management.

Akathisia: Motor restlessness may occur early.

Parkinson Syndrome: Akinesia, characterized by rigidity, immobility and reduction of voluntary movements and tremor, have been observed. Occurrence is less frequent than akathisia.

Dystonic Syndrome: Prolonged abnormal contractions of muscle groups occur infrequently. Symptoms may be managed by the addition of a synthetic antiparkinson agent (other than L-dopa), small doses of sedative drugs, and/or reduction in dosage.

Tardive Dyskinesia: Persistent and sometimes irreversible. See preceeding paragraph under "Warnings."

Autonomic Nervous System: Occasional blurring of vision, tachycardia, nausea, dry mouth and salivation. Urinary retention and constipation may occur, particularly if anticholinergic drugs are used to treat extrapyramidal symptoms.

Laboratory Tests: Rare reports of leucopenia and leucocytosis; treatment with MOBAN may continue if clinical symptoms are absent. Alterations of blood glucose, liver function tests, BUN, and red blood cells have not been considered clinically significant.

Metabolic and Endocrine Effects: Alteration of thyroid function has not been significant. Amenorrhea has been reported infrequently. Resumption of menses in previously amenorrheic women has been reported. Initially heavy menses may occur. Galactorrhea and gynecomastia have been reported infrequently. Increase in libido has been noted in some patients. Impotence has not been reported. Although both weight gain and weight loss have been in the direction of normal or ideal weight, excessive weight gain has not occurred with MOBAN.

Hepatic Effects: There have been rare reports of clinically significant alterations in liver function in association with MOBAN use.

Cardiovascular: Rare, transient, non-specific T wave changes have been reported on EKG. Association with a clinical syndrome has not been established. Rarely has significant hypotension been reported.

Ophthalmological: Lens opacities and pigmentary retinopathy have not been reported. In some patients phenothiazine-induced lenticular opacities have resolved following discontinuation of the phenothiazine while continuing therapy with MOBAN.

Skin: Early non-specific skin rash, probably of allergic origin, has occasionally been reported. Skin pigmentation has not been seen with MOBAN usage alone. MOBAN has certain pharmacological similarities to other antipsychotic agents. Because adverse reactions are often extensions of the pharmacological activity of a drug, all of the known pharmacological effects associated with other antipsychotic drugs should be kept in mind when MOBAN is used. Upon abrupt withdrawal after prolonged high dosage an abstinence syndrome has not been noted.

DOSAGE: Initial and maintenance doses of MOBAN should be individualized. See full prescribing information.

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Contact: Adigala Laxmi, M.D., Acting Clinical Dir., Middletown Psychiatric Center, Office of Mental Health, P.O. Box 1453, Middletown, New York 10940, **(914) 342-5511, extension 3667.**

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Applications are invited from candidates who meet the requirements for the positions of :

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Candidates applying for this position are required to have completed their postgraduate training in Psychiatry with specialty certification and must have three to five years of subsequent clinical experience.

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Candidates applying for this position must have MBBS and M.R.C. Psych (U.K.) or American Board in Psychiatry or equivalent qualifications.

Salary and benefits will be offered commensurate with qualifications, experience and level of responsibility. Candidates intending to pursue a career in Pakistan will be preferred. Applications should include detailed résumé, bibliography and names and addresses of at least three referees familiar with recent work history. Reply to the Personnel Director, P.O. Box 3500, Stadium Road, Karachi-5, Pakistan.

PSYCHIATRY MEDICAL DIRECTOR POSITION

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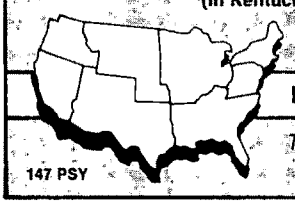
THE POSITION: Medical Director of a 40 bed Adult Program managed by Behavioral Medical Care (BMC), a nationwide psychiatric management firm. This is a salaried position for approximately 20 hours per week. The hospital will provide a competitive financial guarantee, office space, and assistance in setting up private practice.

THE HOSPITAL: The 448 bed full service medical center serves an area of 300,000 individuals living in counties in both Texas and Arkansas. There are three mental health programs managed by BMC in the hospital; a 40-bed adult program, a 24 bed adolescent program, and an adult chemical dependency program. The 150 active medical staff represent most specialties. There are six psychiatrists on active staff.

THE COMMUNITY: This stable community of 70,000 has two colleges nearby and strong public and private school systems. There are numerous cultural and recreational opportunities. The closest medical school is in Shreveport, Louisiana 70 miles away. It is a three hour drive to Dallas and a two hour drive to Little Rock, Arkansas.

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The Queen Elizabeth Hospital is a 601-bed long-term care and rehabilitation institution. There are thirty-two inpatient beds devoted to geriatric psychiatry. The development of a consultation service to other hospital departments, an outpatient assessment programme and a day programme for Alzheimers Disease will all be encouraged. The Toronto General Hospital is a 1000-bed tertiary care teaching institution. Both hospitals are affiliated with the University of Toronto. The Toronto General's Department of Psychiatry operates a large consultation service with close links to other hospital departments. The Consultant Geriatric Psychiatrist will be expected to develop a consultation-liaison programme at Toronto General which can be integrated with both Geriatric Medicine and The Queen Elizabeth Hospital.

Candidates should have their Fellowship in Psychiatry, recognized by the Royal College of Physicians and Surgeons, and specialty training in psychogeriatrics. A special interest in organic brain syndrome is preferred. In addition to organizing clinical services and providing direct patient care, the successful candidate will be involved in teaching medical students and residents in Psychiatry and Geriatric Medicine, and in clinical research. An academic appointment at the appropriate level would occur through the University of Toronto's Department of Psychiatry.

Interested applicants should apply by 13 April 1987 by forwarding a complete curriculum vitae and three references to:

Mr. C.A. Nordal, President,
The Queen Elizabeth Hospital,
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The Psychiatry Service at the Veterans Administration Medical Center, Hampton, Virginia is recruiting for well qualified Psychiatrists. Licensure in any State is acceptable. This JCAH-accredited 450-bed facility has 86 inpatient psychiatry beds as well as an active outpatient department. Our affiliation with the Eastern Virginia Medical School provides the opportunity for an academic appointment, participation in resident and medical student training, and research. Base salary ranges from $62,749-$74,940 contingent upon experience and qualifications. Additional bonus pay up to $11,500 for board certification, full-time employment, and VA tenure. VA Physicians receive 30 days paid vacation, 15 days sick leave, 10 paid holidays and time off for CME activities. Additional benefits include Federal malpractice protection, as well as health and life insurance coverage. The Medical Center is located in the center of Virginia's historic Tidewater area where one can enjoy the stimulation and cultural advantages of urban life along with some of the Sunbelt's most outstanding recreational opportunities.

Contact *Chief, Psychiatry Service, VA Medical Center, Hampton, VA 23667, telephone 804-722-9961, ext 126. An Equal Opportunity Employer.*

DIRECTOR OF CLINICAL SERVICES

One of the leading community mental health/mental retardation centers in the state of Texas is seeking a qualified Director of Clinical Services. The candidate must be a board eligible psychiatrist with administrative experience in a hospital or community psychiatry. This is an excellent opportunity to develop programs and to supervise and train a large multi-disciplinary staff which includes approximately fourteen (14) fulltime equivalent psychiatrists. This center is a comprehensive community mental health services provider.

The position affords an exceptional opportunity to participate in a front running organization.

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Please direct Vitae to:

Bexar County Mental Health
Mental Retardation
Attn: Personnel Director
434 So. Main, Suite 400
San Antonio, Texas 78204

CHAIRPERSON
Department of Psychiatry

The Long Island Jewish Medical Center is seeking a Chairperson for its Department of Psychiatry. Located on 47 acres, the medical center has 3 major clinical divisions including the 223-bed Hillside Hospital & is a designated NIMH Clinical Research Center for the study of schizophrenia.

The successful candidate will be a senior academic psychiatrist able to assume responsibility for the 223-bed Hillside Hospital division; the Schneider Children's Hospital division with its 15-bed inpatient unit & ambulatory programs; & the Long Island Jewish Hospital with its liaison & consultation service as well as its psychiatric emergency room. Through an affiliation contract with the New York City Health and Hospitals Corporation, the chairperson will also have responsibility for the Queens Hospital Center's Department of Psychiatry.

The successful candidate will have a developed research interest & be eligible for a medical school appointment at the professorial level. The candidate will have extensive teaching experience & will also be able to utilize his/her expertise for the planning of a major new physical facility. **Submit inquiries to: Chairperson, Department of Psychiatry Search Committee, c/o Robert K. Match, MD, President.**

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POSITION AVAILABLE

DIRECTOR, NATIONAL INSTITUTE OF MENTAL HEALTH, ALCOHOL, DRUG ABUSE, AND MENTAL HEALTH ADMINISTRATION
PUBLIC HEALTH SERVICE
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The Alcohol, Drug Abuse, and Mental Health Administration invites nominations and applications for the position of Director, National Institute of Mental Health (NIMH).

This is a Senior Executive Service position in the career Civil Service, with an annual salary range of $63,200 to $72,500. Physicians may also be eligible for a Physicians' Comparability Allowance of up to $10,000 per year. The position is located in Rockville, Maryland.

The National Institute of Mental Health provides leadership for the Federal effort in the promotion of mental health. Its programs include intramural and extramural research, the administration of training programs to meet national mental health manpower needs, and the provision of technical services to States and communities. The Director manages a staff of 1,000 and a budget of $342 million.

Minimum qualifications requirements include a degree of Doctor of Medicine, Doctor of Osteopathy, or a bachelor's or higher degree in an academic field relating to the health sciences, and progressively responsible experience in developing, administering, and evaluating mental health programs. Candidates must also have experience in the management of mental health programs, demonstrating competence to assume leadership in planning, staffing, directing, coordinating and allocating resources, and other responsibilities associated with executive leadership of a major national program.

Further information about the position and qualification requirements may be obtained by contacting Ms. Lois Mercer at 301/443-5030. Applications (Application for Federal Employment, SF 171) accompanied by a current curriculum vitae and bibliography should be submitted to Ms. Mercer at the Division of Personnel Management, Alcohol, Drug Abuse, and Mental Health Administration, 5600 Fishers Lane, Room 15C-26, Rockville, Maryland 20857. Applications will be accepted without the SF 171, provided that the SF 171 is submitted upon request. Nominations and applications should be submitted by March 9, 1987.

Applications from women and minority group members are especially solicited.

THE ALCOHOL, DRUG ABUSE. AND MENTAL HEALTH ADMINISTRATION IS AN EQUAL OPPORTUNITY EMPLOYER.

THE DEPARTMENT OF PSYCHIATRY AT THE UNIVERSITY OF VERMONT AND THE MEDICAL CENTER HOSPITAL OF VERMONT is seeking a Clinical Director for inpatient psychiatry services. The Clinical Director is a full-time faculty member of the university and should be board certified and have prior experience in acute inpatient psychiatric care with research and training in a university setting. The Medical Center Hospital of Vermont is the major teaching hospital of the College of Medicine and is the tertiary referral center for Vermont, northern New England and New York. This is an excellent academic position in a most desirable setting.

Application Deadline:
June 1, 1987

Starting Date:
July 1, 1987

Contact:
Sheldon Weiner, M.D.
Professor and Chairman
Department of Psychiatry
University of Vermont College of Medicine
Burlington, Vermont 05405

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New! **THE PREDICTION OF CRIMINAL VIOLENCE** *edited by* **Fernand N. Dutile** *and* **Cleon H. Foust.** Experts in the field present their positions and viewpoints regarding prediction in both the criminal and juvenile justice systems. They explore legal and ethical limits on the use of predictions of dangerousness, clinical applicability for prediction, diversion from prosecution, attempts to predict pretrial violence, and criminal violence prediction for juveniles. Selected roundtable discussions explore preventive detention, probation and parole, and the amount of bail. *'87, $34.75*

New! **THE ANATOMY OF ILLUSION: Religious Cults and Destructive Persuasion** *by* **Thomas W. Keiser** *and* **Jacqueline L. Keiser.** This unique theoretical orientation dispels much of the confusion and mystique surrounding the cult experience. The authors answer common questions—What is a cult? Who joins cults and why? Who is vulnerable to their manipulations?—and addresses the legal implications, such as the rights of cult members and the risks of coercive deprogramming. *Feb. '87, about $25.25*

New! **FUNDAMENTALS OF MARKETING THE PRIVATE PSYCHOTHERAPY PRACTICE** *by* **Bruce D. Forman** *and* **Kadette S. Forman.** Devoted solely to concerns of private mental health services, this book covers the marketing concept; marketing strategies; techniques for analyzing, monitoring, and auditing a private practice; and the marketing mix (place, price, product, and promotion). An entire chapter explores the topic of promotion, including copywriting, layout design, and direct mail advertising. The authors also examine relevant ethical principles. *Mar. '87, about $27.25*

PSYCHOTHERAPY FOR MEN: Transcending the Masculine Mystique *by* **Robert Allan Silverberg.** The author examines the destructive effects of the traditional male socialization process, and he shows how such conditioning creates therapeutic obstacles for those men who seek professional help. The text offers numerous therapeutic approaches and techniques to help men achieve better balance in their lives and better relationships with women and with other men. *'86, $32.75*

A PRACTICAL GUIDE TO PSYCHODIAGNOSTIC TESTING *by* **Lawrence Katz.** From a strictly clinical orientation, the author conveys his views on psychodiagnostic testing. The vast experience on which he draws imbues in the text an authority that will help readers better understand the field. He considers testing under nonstandard conditions, interpreting tests for major diagnostic categories, examining for treatment readiness, examining for disability or incompetency, report writing, and major issues in psychodiagnostic testing. *'85, $27.00*

THE CLINICAL PSYCHOLOGY OF MELANIE KLEIN *by* **O. Weininger.** Written for professionals with little background in psychoanalysis, this text presents Melanie Klein's contributions to the understanding of childhood development, psychopathology and treatment. Her theories on birth trauma and early mother-child interaction, ego development and object relations, and the Oedipal phase are detailed. A list of the writings of Melanie Klein and an illustration of play psychotherapy within a Kleinian framework conclude the text. *'84, $25.25*

New! **THE HANDBOOK OF PATHOLOGICAL GAMBLING** *edited by* **Thomas Galski.** Herein the contributors, all veritable pioneers in the treatment of compulsive gambling, provide the theoretical framework for effective diagnosis, treatment and rehabilitation. Salient personality variables of the pathological gambler, family dynamics, pathological gambling and crime, physiological determinants, psychological testing (research, uses and new directions), and treatment and rehabilitation are all thoroughly reviewed. *'87, $30.25*

New! **ACTIVITIES FOR CHILDREN IN THERAPY: A Guide for Planning and Facilitating Therapy with Troubled Children** *by* **Susan T. Dennison** *and* **Connie K. Glassman.** More than 200 creative activities are presented for professional use with children between the ages of five and twelve. These concrete ideas for intervention cover six content areas: relationship building and self-disclosure, affective awareness and communication, family, social skills, school, termination and follow-up. An individual therapy practice model and informative appendices complement the text. *Feb. '87, about $32.75*

New! **CLINICAL RESEARCH IN SCHIZOPHRENIA** *edited by* **Roy R. Grinker, Sr.** *and* **Martin Harrow.** This book opens with a theoretical overview of schizophrenia and follows with research results on diagnosis and psychopathology, and on thought disorder and negative-deficit symptoms. The prognosis and outcome in schizophrenia and other severe psychiatric disorders are also discussed. The text concludes with a review of the major aspects of the overall research program. *July '87, about $55.00*

THE DIFFERENTIAL DIAGNOSTIC TECHNIQUE—A VISUAL MOTOR PROJECTIVE TEST: Research and Clinical Use *by* **Otto Weininger.** This test contains twelve figures (straight-line, curved-line, and mixed straight- and curved-line figures) on stimulus cards for use with the child or adult. An interpretive structure of psychoanalytic symbolism is provided. The quantitative scores which result also allow for objective analysis. Reliability and validity studies, as well as individual case examples and interpretations, are included. *'86, $27.25*

HYPNOSIS COMPLICATIONS: Prevention and Risk Management *by* **Frank J. MacHovec.** This informative book focuses on the unexpected problems and complications of hypnosis. Risk evaluation; itemized risk factors related to subjects, hypnotists and the environment; malpractice; and risk management including crisis intervention all receive in-depth coverage. Appendices include data sheets and checklists, informed consent/treatment contracts, treatment summary, and a complications report form. *'86, $24.75*

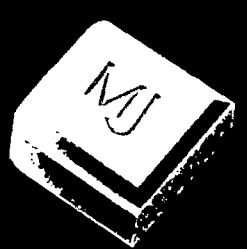
THE CLINICAL APPLICATION OF PROJECTIVE DRAWINGS (6th Ptg.) *by* **Emanuel F. Hammer.** Intelligent and insightful, this book covers fundamentals, differential diagnosis, appraisal of psychodynamics, conflict and defense, psychological resources as treatment potentials, and projective drawing usage in therapy. The text includes in its integrated presentation the Draw-A-Family procedure, Harrower's Unpleasant Concept Test, Kinget's Drawing Completion Test, and the Eight Card Redrawing Test, among many others. *'80, $38.25*

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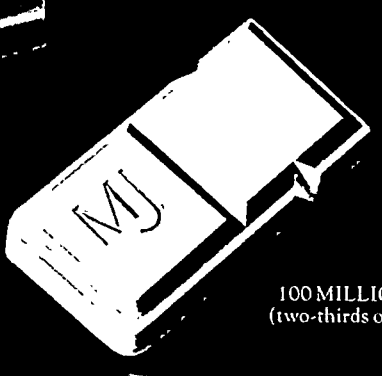
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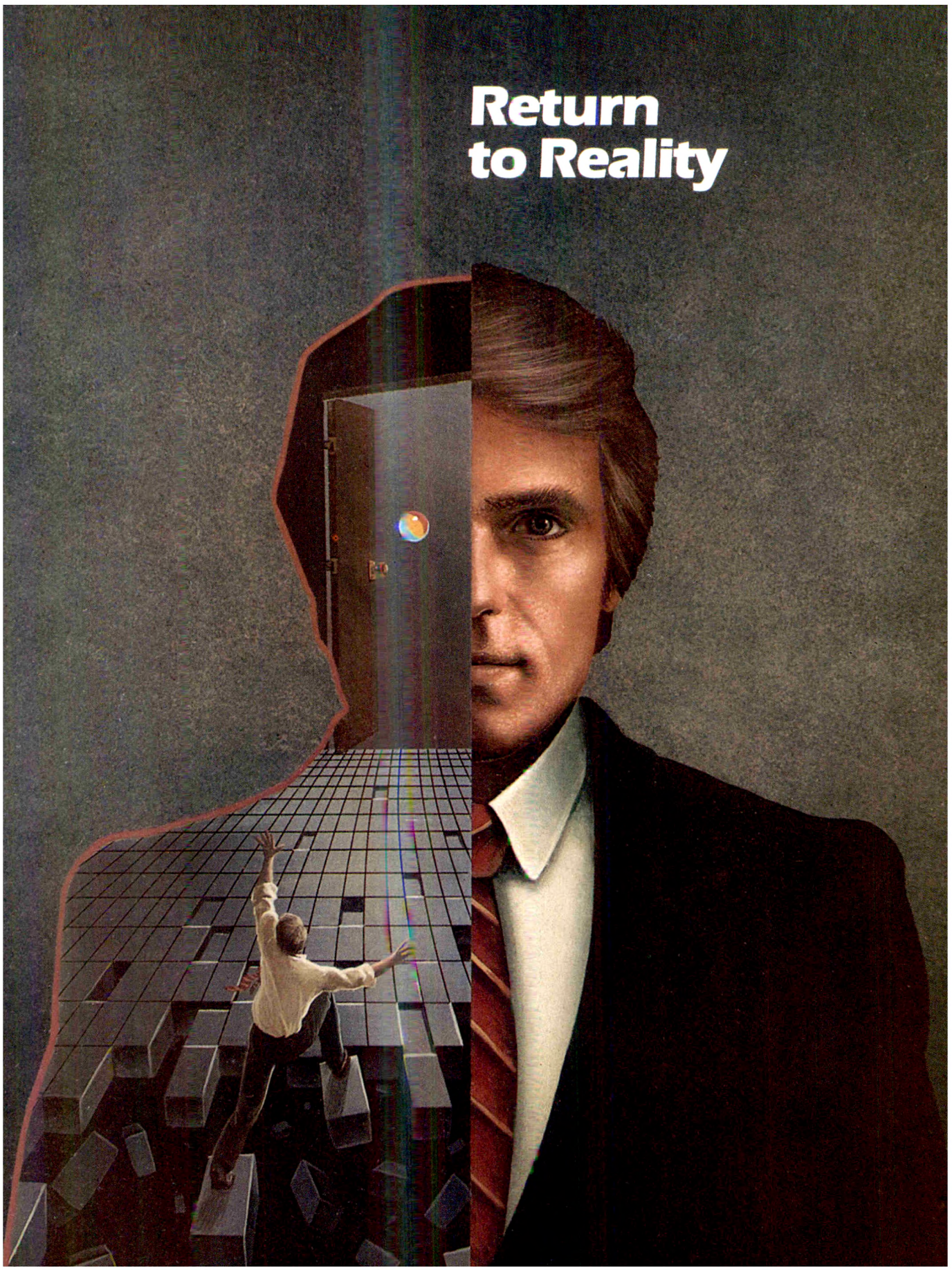
THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 144, Number 4 April 1987

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Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. (See PRECAUTIONS.)

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent in vitro, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

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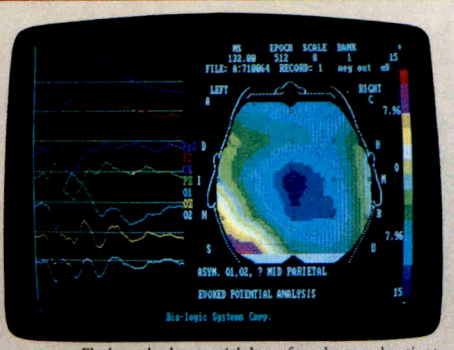
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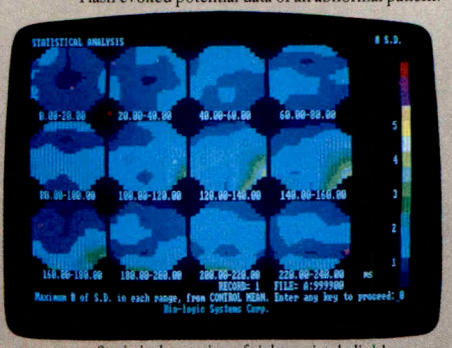
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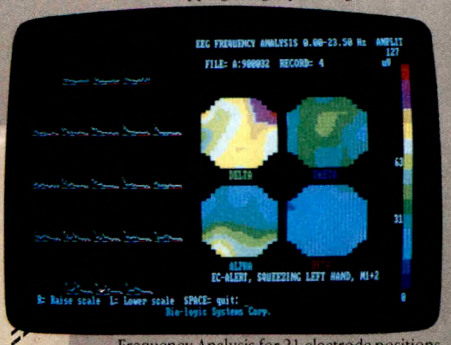
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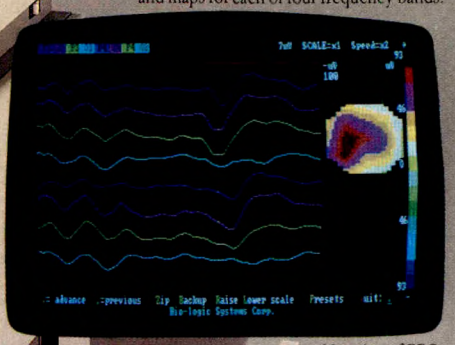
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The American Journal of Psychiatry, ISSN 0002-953X, is published monthly by the American Psychiatric Association, 1400 K Street, N.W., Washington, DC 20005. Subscriptions: U.S. $50.00 per year, Canada and foreign $65.00; single issues: U.S. $7.00, Canada and foreign $8.00.

Business communications, changes of address, and questions about subscriptions from APA members should be directed to the Division of Member Services: (202) 682-6090. Communications from nonmember subscribers should be directed to the Circulation Department: (202) 682-6158. Authors who wish to contact the *Journal* editorial office should call (202) 682-6020.

Business Management: Nancy Frey, Director, Periodicals Services; Laura G. Abedi, Advertising Production Manager: (202) 682-6154; Beth Prester, Director, Circulation; Karen Loper, Promotion Manager; Jackie Coleman, Fulfillment Manager.

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Type set by Byrd PrePress, 5408 Port Royal Road, Springfield, VA 22151. Printed by Dartmouth Printing Company, 69 Lyme Road, Hanover, NH 03755.

Second-class postage paid at Washington, DC, and additional mailing offices. POSTMASTER: Send address changes to Circulation Department, American Psychiatric Association, 1400 K Street, N.W., Washington, DC 20005.

Indexed in *Abstracts for Social Workers, Biological Abstracts, Chemical Abstracts, Chicago Psychoanalytic Literature Index, Cumulative Index to Nursing Literature, Excerpta Medica, Hospital Literature Index, Index Medicus, International Nursing Index, Nutrition Abstracts, Psychological Abstracts, Science Citation Index,* and *Social Sciences Index.*

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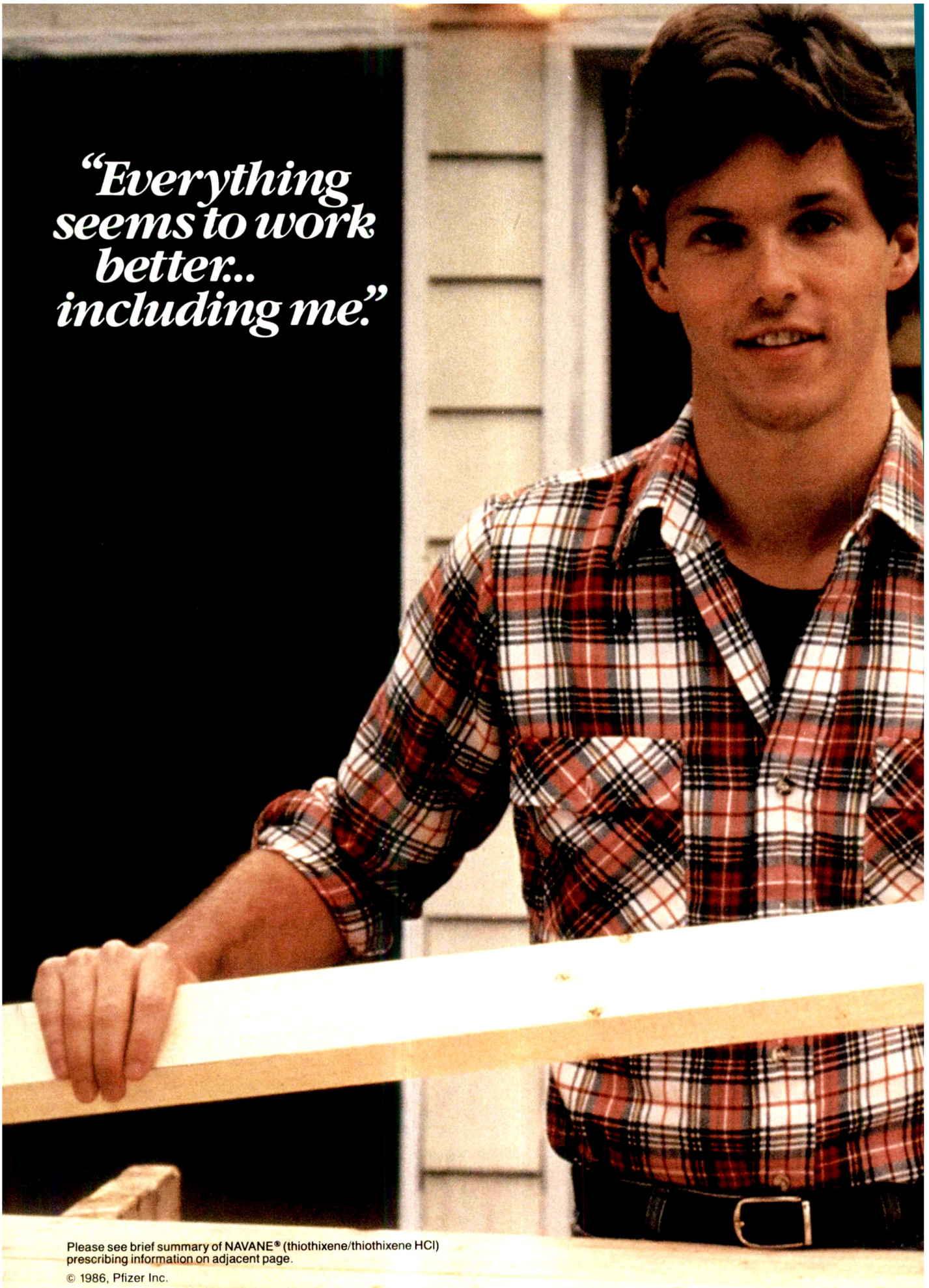
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Please see brief summary of NAVANE® (thiothixene/thiothixene HCl) prescribing information on adjacent page.

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References: 1 Bressler B, Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. **2** DiMascio A, Demirgian E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. **3** DiMascio A, Demirgian E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association. Washington, DC, May 3-6, 1971. **4** Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients, in Lehmann HE, Ban TA (eds): *The Thioxanthenes: Modern Problems of Pharmacopsychiatry.* Basel, Switzerland, S Karger, 1969, vol 2, pp 45-52. **5** Dillenkofter RL, Gallant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented as a Scientific Exhibit at The 125th Annual Meeting of The American Psychiatric Association, Dallas, May 1-4, 1972. **6** Data available on request from Roerig.

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
(thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml

Contraindications: Navane (thiothixene) is contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Navane is contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treament, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the section on Adverse Reactions.)

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long term therapy or may occur after drug therapy has been discontinued. The risk seems to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage and Administration: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. In general, small doses should be used initially and gradually increased to the optimal effective level, based on patient response.

Some patients have been successfully maintained on once-a-day Navane therapy.

Usage in children under 12 years of age is not recommended because safe conditions for its use have not been established.

Navane Intramuscular Solution: Navane For Injection—When more rapid control and treatment of acute behavior is desirable, the intramuscular form of Navane may be indicated. It is also of benefit where the very nature of the patient's symptomatology, whether acute or chronic, renders oral administration impractical or even impossible.

For treatment of acute symptomatology or in patients unable or unwilling to take oral medication, the usual dose is 4 mg of Navane Intramuscular administered 2 to 4 times daily. Dosage may be increased or decreased depending on response. Most patients are controlled on a total daily dosage of 16 to 20 mg. The maximum recommended dosage is 30 mg/day. An oral form should supplant the injectable form as soon as possible. It may be necessary to adjust the dosage when changing from the intramuscular to oral dosage forms. Dosage recommendations for Navane (thiothixene) Capsules and Concentrate appear in the following paragraphs.

Navane Capsules: Navane Concentrate—In milder conditions, an initial dose of 2 mg three times daily. If indicated, a subsequent increase to 15 mg/day total daily dose is often effective.

In more severe conditions, an initial dose of 5 mg twice daily.

The usual optimal dose is 20 to 30 mg daily. If indicated, an increase to 60 mg/day total daily dose is often effective. Exceeding a total daily dose of 60 mg rarely increases the beneficial response.

Overdosage: Manifestations include muscular twitching, drowsiness, and dizziness. Symptoms of gross overdosage may include CNS depression, rigidity, weakness, torticollis, tremor, salivation, dysphagia, hypotension, disturbances of gait, or coma.

Treatment: Essentially is symptomatic and supportive. For Navane oral, early gastric lavage is helpful. For Navane oral and Intramuscular, keep patient under careful observation and maintain an open airway, since involvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overdosage. If hypotension occurs, the standard measures for managing circulatory shock should be used (I.V. fluids and/or vasoconstrictors.)

If a vasoconstrictor is needed, levarterenol and phenylephrine are the most suitable drugs. Other pressor agents, including epinephrine, are not recommended, since phenothiazine derivatives may reverse the usual pressor action of these agents and cause further lowering of the blood pressure.

If CNS depression is present and specific therapy is indicated, recommended stimulants include amphetamine, dextroamphetamine, or caffeine and sodium benzoate. Stimulants that may cause convulsions (e.g. picrotoxin or pentylenetetrazol) should be avoided. Extrapyramidal symptoms may be treated with antiparkinson drugs.

There are no data on the use of peritoneal or hemodialysis, but they are known to be of little value in phenothiazine intoxication.

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Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, *1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to* Journal *readers will be included.*

JUNE

June 3–6, annual meeting, National Council of Community Mental Health Centers, Miami Beach, Fla. Contact Frank H. Bailey, Executive Director, 6101 Montrose Rd., Suite 360, Rockville, MD 20852; 301-984-6200.

June 4–6, annual conference, Society for Menstrual Cycle Research, Ann Arbor, Mich. Contact Nancy Reame, Ph.D., R.N., Program Director, Parent-Child Nursing, University of Michigan, 400 N. Ingalls, Ann Arbor, MI 48109; 313-763-0016.

June 10–12, Tenth International Meeting of the Harry Benjamin International Gender Dysphoria (Transsexualism) Society, Amsterdam. Contact Aaron Billowitz, M.D., Program Chairman, 3395 Scranton Rd., Cleveland, OH 44109; 216-459-4605.

June 11–14, annual meeting, American Association of Neuropathologists, Seattle. Contact James M. Powers, M.D., Executive Director, MUSC Dept. of Pathology, 171 Ashley Ave., Charleston, SC 29452; 803-792-3581.

June 14–18, annual meeting, National League for Nursing, Washington, D.C. Contact Pamela J. Maraldo, Ph.D., R.N., Executive Director, 10 Columbus Circle, New York, NY 10019; 212-582-1022.

June 14–19, 6th International Catecholamine Symposium, Jerusalem. Contact Prof. R. Haim Belmaker, Chairman, P.O. Box 983, Jerusalem, 91009, Israel; 02-527335; Telex 341171 KENS IL.

June 15–19, annual meeting, Committee on Problems of Drug Dependence, Philadelphia. Contact William L. Dewey, Ph.D., Chairman, P.O. Box 613, MCV Station, Richmond, VA 23298; 804-786-8406.

June 18–19, annual meeting, Association of Directors of Medical Student Education in Psychiatry, Denver. Contact Deborah C. Roth, D.O., Dept. of Psychiatry, Box 14, University of South Florida, 12901 N. 30th St. Tampa, FL 33612; 813-974-4242.

June 19–20, annual meeting, National Congress of Parents and Teachers, Dallas. Contact Robert N. Woerner, Executive Administrator, 700 N. Rush St., Chicago, IL 60611; 312-787-0977.

June 21–25, annual meeting, American Medical Association, Chicago. Contact James H. Sammons, M.D., Executive Vice-President, 535 N. Dearborn St., Chicago, IL 60610; 312-645-5000.

June 22–25, annual meeting, British Medical Association, Bristol, United Kingdom. Contact Dr. J.D.J. Harvard, Secretary, BMA House, Tavistock Square, London, WC1M 9JP, United Kingdom; 01-387-4499.

June 26–28, annual meeting, The Huxley Institute for Biosocial Research, Atlanta. Contact Mary E. Haggerty, Executive Director, 900 N. Federal Hwy., Suite 330, Boca Raton, FL 33432; 303-393-6167, 800-847-3802.

June 28–July 3, annual meeting, Sleep Research Society, Copenhagen. Contact J. Christian Gillin, M.D., Executive Secretary, Dept. of Psychiatry, M003, University of California, S.D., La Jolla, CA 92037; 619-452-2137.

June 30–July 2, annual meeting, Royal College of Psychiatrists, Belfast. Contact Dr. Thomas H. Bewley, President, 17 Belgrave Square, London, SW1X 8PG, United Kingdom; 01-235-2351.

JULY

July 19–24, First International Symposium on Management of Pain, Stress, Fear and Anxiety, Tel-Aviv, Israel. Contact Prof. Y. Sharav, Hebrew University-Hadassah, P.O. Box 1172, Jerusalem, 91010, Israel; 972-2-446146.

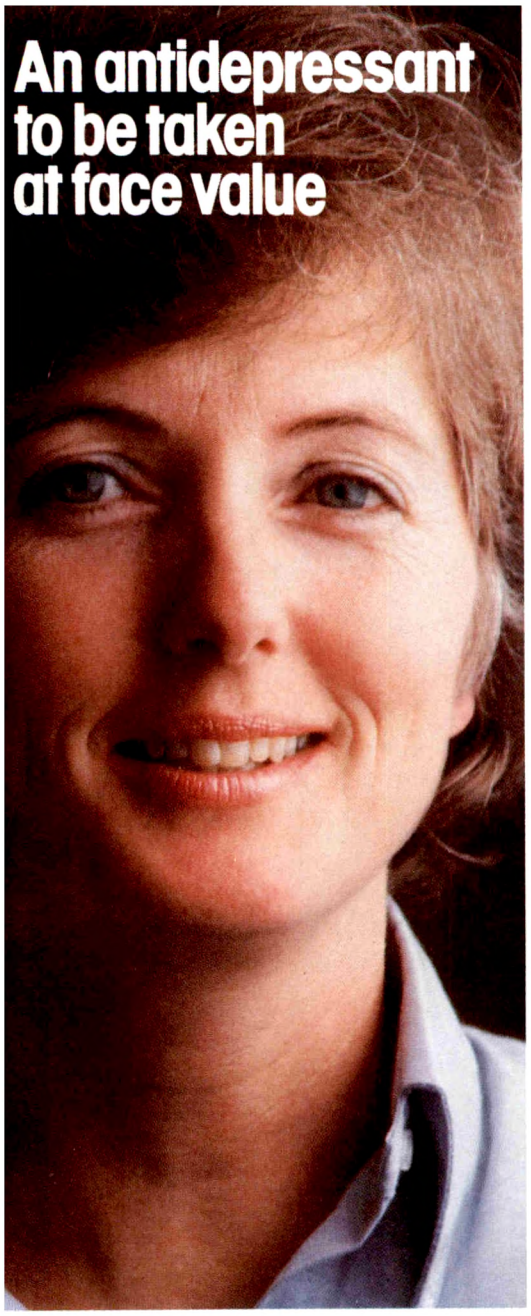
July 31–August 2, 8th Biennial MRI Conference, Solutions-Pseudosolutions-Ultrasolutions, San Francisco. Contact MRI Conference, 555 Middlefield Rd., Palo Alto, CA 94301; 415-321-3055.

AUGUST

August 2–6, annual conference, African Psychiatric Association, Harare, Zimbabwe. Contact Godfrey Huggins, School of Medicine, P.O. Box A 178, Avondale, Harare, Zimbabwe.

August 3–5, annual convention, American Hospital Association, Philadelphia. Contact H. Joseph Curl, Executive Vice-President, 840 North Lake Shore Dr., Chicago, IL 60611; 312-280-6000.

(Continued on page A34)



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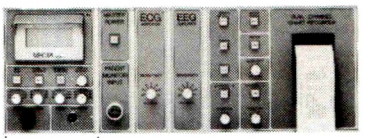
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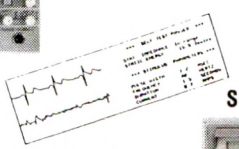
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TOPICS AND SPEAKERS

■ Management of the Intractably Psychotic Patient
John R. Lion, M.D.
Clinical Professor of Psychiatry
University of Maryland School of Medicine
Institute of Psychiatry and Human Behavior
Baltimore, Maryland

■ Maintenance Treatment Strategies Focusing on Psychopharmacologic Issues
John M. Kane, M.D.
Professor of Psychiatry
School of Medicine Health Sciences Center
State University of New York at Stony Brook
Long Island, New York

Director, Psychiatric Research
Hillside Division of Long Island Jewish
Medical Center
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■ Psychosocial Intervention in the Management of Schizophrenia: Overcoming Disability and Handicap
Robert P. Liberman, M.D.
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University of California at Los Angeles
Los Angeles, California

Director, Clinical Research Center for
Schizophrenia and Psychiatric Rehabilitation
Chief, Rehabilitation Services
Brentwood Division of the West Los Angeles
VA Medical Center
Los Angeles, California

Director, Clinical Research Unit
Camarillo State Hospital
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■ The Schizophrenic Patient: Living with a Chronic Disorder in a Changing Social Environment
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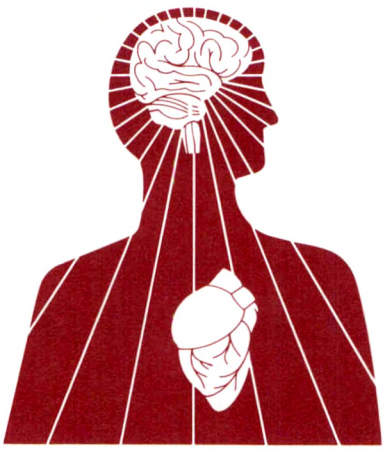
"Cardiovascular symptoms are generally the most prominent — and most frightening — symptoms of panic disorder. Also, several studies suggest that as many as 35% to 50% of panic disorder patients have mitral valve prolapse. Patients so frequently seek consultation for their symptoms that they may constitute one third of all cardiology patients. Proper evaluation and management of cardiovascular symptoms are central to the care of panic disorder patients."

James C. Ballenger, MD

The Medical University of South Carolina announces a symposium at the 140th Annual Meeting of the American Psychiatric Association

Cardiovascular Aspects of Anxiety: The Controversies and Concerns

Sunday, May 10, 1987
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Because several recent studies suggest that many panic disorder patients also have mitral valve prolapse (MVP), cardiovascular symptoms in patients with anxiety are a growing concern to psychiatrists today. Although controversy surrounds the frequency of occurrence of these symptoms, the importance of cardiology knowledge applied to the practice of psychiatry cannot be overlooked.

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Program

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Introduction
James C. Ballenger, MD
Professor and Chairman
Department of Psychiatry and Behavioral Sciences
Medical University of South Carolina
Charleston, South Carolina

Mitral Valve Prolapse: A Basis for Diagnostic Classification
Charles F. Wooley, MD
Professor of Medicine
Director of the Cardiovascular Teaching and Research Laboratories
Ohio State University
Columbus, Ohio

Prevalence of MVP in Panic Disorder
Richard R. Liberthson, MD
Associate Professor of Pediatrics
Harvard Medical School
Pediatrician and Associate Physician of the Cardiac Unit
Department of Cardiology
Massachusetts General Hospital
Boston, Massachusetts

MVP in Panic Disorder Patients
James C. Ballenger, MD

Summary Remarks
Charles F. Wooley, MD

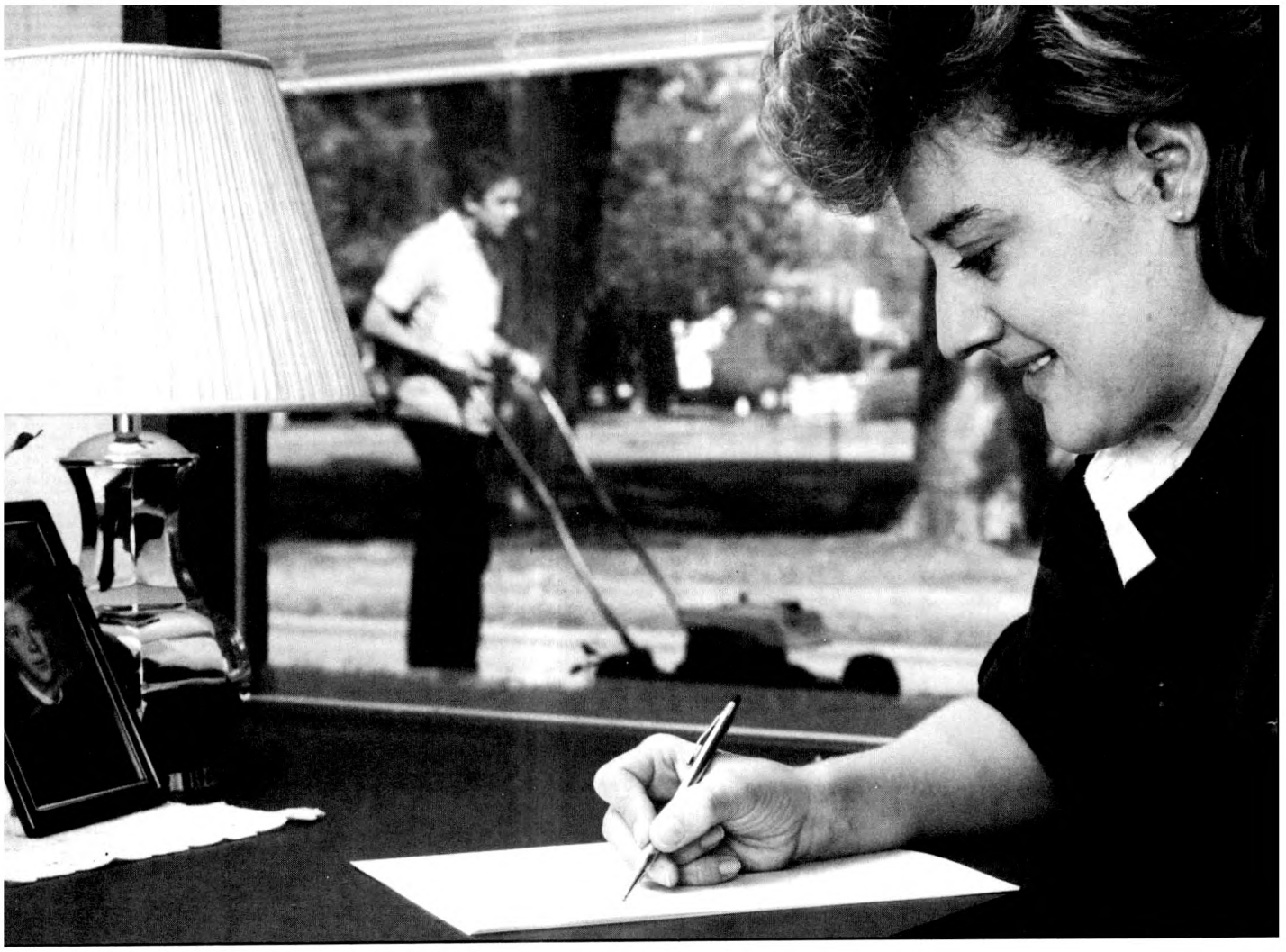
Monitoring Devices: An Overview
Andrew P. Selwyn, MD
Associate Professor of Medicine
Harvard Medical School
Director, Cardiac Catheterization Lab
Cardiovascular Division
Brigham & Women's Hospital
Boston, Massachusetts

Ambulatory Monitoring of Panic Attacks
Walton T. Roth, MD
Professor of Psychiatry and Behavioral Science
Department of Psychiatry
Stanford University
Stanford, California
Chief of Psychiatry Consultation Service
Palo Alto VA Medical Center
Palo Alto, California

Panic Disorder, Chest Pain, and Cardiology Patients
Bernard D. Beitman, MD
Associate Professor of Psychiatry
Department of Psychiatry
University of Missouri
Columbia, Missouri

Angina Pectoris and Asymptomatic Ischemia
Andrew P. Selwyn, MD

Panel Discussion



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WARNINGS: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increases. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low dosages.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome, and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dosage and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

Mental and/or physical abilities may be impaired, especially during early therapy; warn ambulatory patients about activities requiring alertness, about concomitant use of alcohol and other CNS depressants. Not recommended for management of behavioral complications in mentally retarded patients.
PRECAUTIONS: Use with extreme caution in patients with a history of convulsive disorders; seizures have been reported in epileptic patients receiving antipsychotic dosage levels and in epileptic patients with maintenance of anticonvulsant therapy. Use with caution in patients with cardiovascular disease or in those with glaucoma or a tendency to urinary retention, particularly when on concomitant anticholinergic medication. Loxapine has an antiemetic effect in animals which might occur in man, masking signs of overdosage of toxic drugs and obscuring intestinal obstruction or brain tumor. Since possible ocular toxicity cannot be excluded, observe carefully for pigmentary retinopathy and lenticular pigmentation. Slightly higher incidence of extrapyramidal effects possible following IM administration than normally anticipated with oral formulations.

Neuroleptic drugs elevate prolactin levels; elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Safe use during pregnancy or lactation or by women of child-bearing potential has not been established; weigh potential benefits against possible risks to mother and child. No embryotoxicity or teratogenicity was observed in studies in rats, rabbits, or dogs, although, with the exception of one rabbit study, the highest dosage was only two times the maximum recommended human dosage, and in some studies it was below this dosage. Perinatal studies have shown renal papillary abnormalities in offspring of rats treated from midpregnancy with doses of 0.6 to 1.8 mg/kg doses which approximate the usual human dose but which are considerably below the maximum recommended human dose. It is known that this drug and its metabolites have been transported into the milk of lactating dogs. LOXITANE® *loxapine* administration to nursing women should be avoided, if clinically possible. Not recommended for use in children under 16.
ADVERSE REACTIONS: *CNS Effects;* Other than extrapyramidal, have been seen infrequently. Drowsiness, dizziness, faintness, staggering gait, shuffling gait, muscle twitching, weakness, insomnia, agitation, tension, seizures, akinesia, slurred speech, numbness, and confusional states have been reported. Neuroleptic malignant syndrome (NMS) has been reported. *Extrapyramidal Reactions:* Neuromuscular (extrapyramidal) frequently, often during the first few days of treatment. Reactions involved parkinsonian-like symptoms such as tremor, rigidity, excessive salivation, and masked facies. Akathisia (motor restlessness) also has been reported relatively frequently. Dystonic and dyskinetic reactions have occurred less frequently, but may be more severe. Dystonias include spasms of muscles of the neck and face, tongue protrusion, and oculogyric movement. Dyskinetic reactions have been described in the form of choreoathetoid movements. These reactions sometimes require reduction or temporary withdrawal of loxapine dosage in addition to appropriate counteractive drugs.

Persistent Tardive Dyskinesia: As with all antipsychotic agents, tardive dyskinesia may appear in some patients on long-term therapy or may appear after drug therapy has been discontinued. Risk appears to be especially greater in elderly female patients on high-dosage therapy. Symptoms are persistent and in some patients appear to be irreversible. Syndrome is characterized by rhythmical involuntary movement of the tongue, face, mouth, or jaw (eg, protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities. *Cardiovascular Effects:* Tachycardia, hypotension, hypertension, orthostatic hypotension, lightheadedness, and syncope. A few cases of ECG changes have been reported. *Hematologic:* Rarely, agranulocytosis, thrombocytopenia, leukopenia. *Skin:* Dermatitis, edema (puffiness of face), pruritus, rash, alopecia, and seborrhea. *Anticholinergic Effects:* Dry mouth, nasal congestion, constipation, blurred vision, urinary retention, and paralytic ileus. *Gastrointestinal:* Nausea, vomiting, and hepatocellular injury (ie, SGOT/SGPT elevation). Rarely, jaundice and/or hepatitis. *Other:* Weight gain, weight loss, dyspnea, ptosis, hyperpyrexia, flushed facies, headache, paresthesia, and polydipsia. Rarely, galactorrhea, amenorrhea, gynecomastia, and menstrual irregularity of uncertain etiology.
OVERDOSAGE: Signs and symptoms are those expected from the pharmacological actions and amount ingested. Can range from mild depression of CNS and cardiovascular symptoms to profound hypotension, respiratory depression and unconsciousness. Extrapyramidal symptoms and convulsive seizures have occurred as well as renal failure. Treatment is essentially symptomatic and supportive. Early gastric lavage with dialysis might be expected to be beneficial. *Avoid* use of centrally acting emetics, analeptics, and epinephrine.

Rev. 1/86

References:

1. Thompson TL II, Moran MG, Nies AS: Psychotropic drug use in the elderly. *New Engl J Med* 1983; 308:194-199.
2. Rhoades HM, Overall JE: Side effect potentials of different antipsychotic and antidepressant drugs. *Psychopharmacol Bull* 1984; 20:83-88.
3. Data on file, Lederle Laboratories, Pearl River, N.Y.

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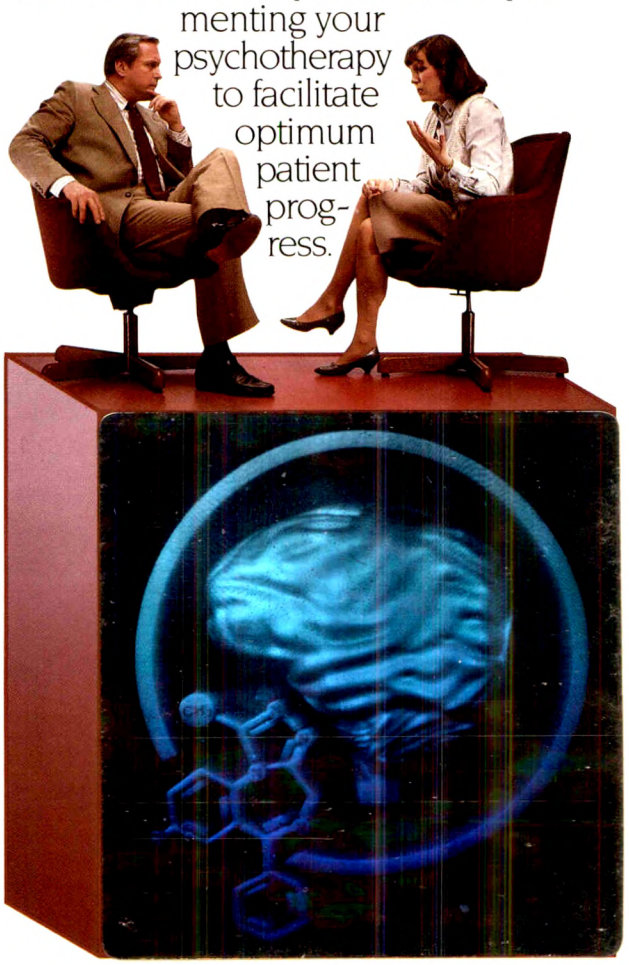
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Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or lightheadedness.

Central nervous system. Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

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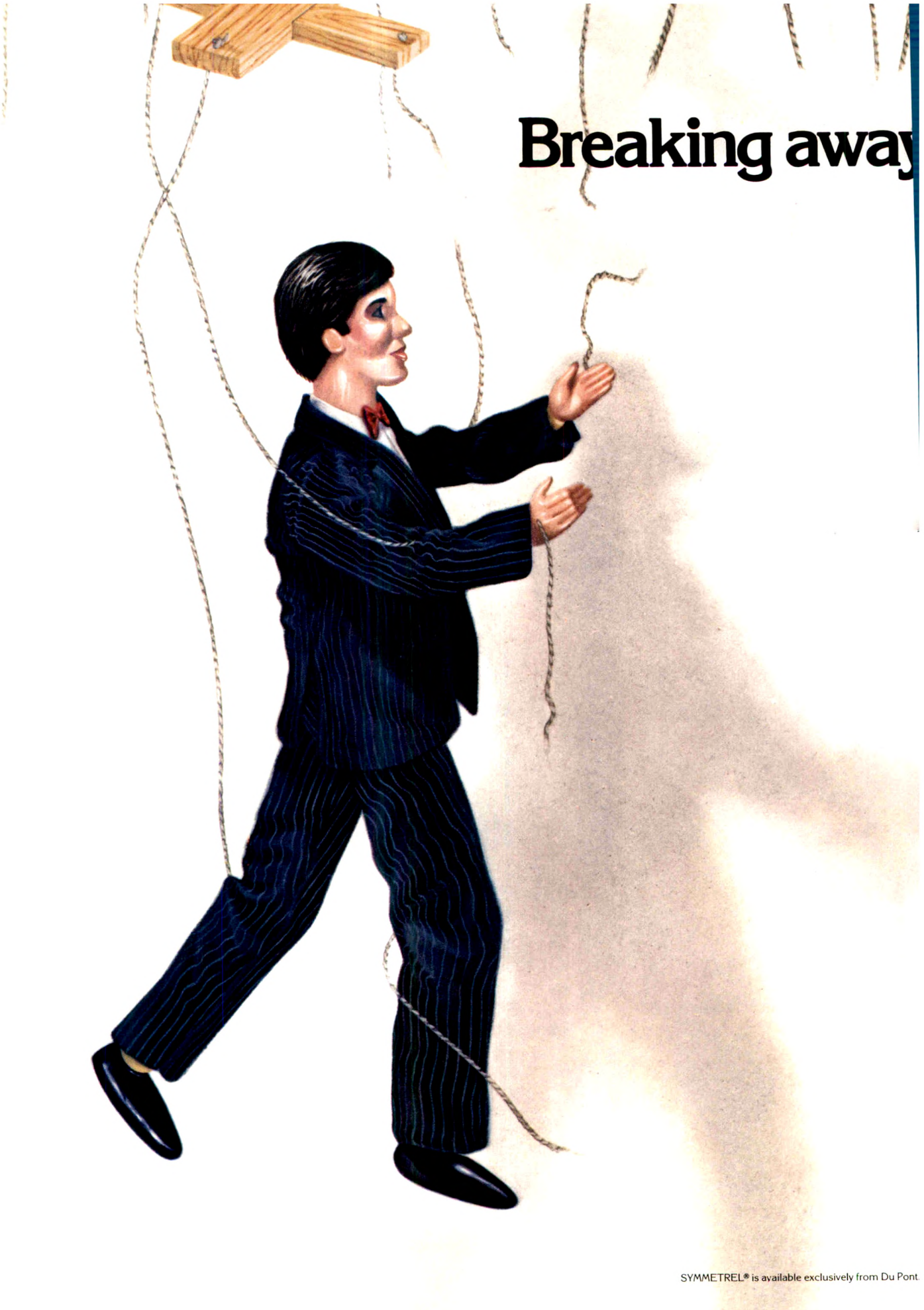
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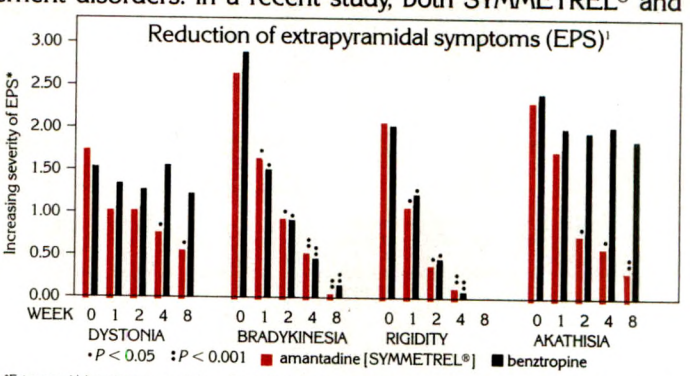


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*Extrapyramidal symptoms were rated on a four-point scale of ascending severity. —adapted from Borison and Diamond, p 42[1]

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Dramatically differentiating SYMMETREL® from anticholinergics is its favorable side effect profile. With fewer anticholinergic side effects, SYMMETREL® affords patients greater comfort—encouraging compliance with their antipsychotic regimen. SYMMETREL® is not metabolized and is mainly excreted in the urine. Care should be taken, however, in patients with renal impairment. SYMMETREL®. The more rational and safer[1] therapeutic choice in the control of EPS.

Incidence of anticholinergic side effects[1]

	% patients taking amantadine	% patients taking benztropine
Dry mouth	7.4	41.6
Blurred vision	2.6	26.5
Nasal congestion	2.5	18.2
Constipation	1.8	21.4
Urinary hesitancy	1.3	7.1

—adapted from Borison and Diamond, p 43[1]

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[AMANTADINE HCl]

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE: *Parkinson's Disease/Syndrome and Drug-Induced Extrapyramidal Reactions:* SYMMETREL is indicated in the treatment of idiopathic Parkinson's disease (Paralysis Agitans), postencephalitic parkinsonism, drug-induced extrapyramidal reactions, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication. It is indicated in those elderly patients believed to develop parkinsonism in association with cerebral arteriosclerosis. In the treatment of Parkinson's disease, SYMMETREL is less effective than levodopa, (-)-3-(3, 4-dihydroxyphenyl)-L-alanine, and its efficacy in comparison with the anticholinergic antiparkinson drugs has not yet been established. Although anticholinergic type side effects have been noted with SYMMETREL when used in patients with drug-induced extrapyramidal reactions, there is a lower incidence of these side effects than that observed with anticholinergic antiparkinson drugs.

CONTRAINDICATIONS: SYMMETREL is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Patients with a history of epilepsy or other "seizures" should be observed closely for possible increased seizure activity.

Patients with a history of congestive heart failure or peripheral edema should be followed closely as there are patients who developed congestive heart failure while receiving SYMMETREL.

Patients with Parkinson's disease improving on SYMMETREL should resume normal activities gradually and cautiously, consistent with other medical considerations, such as the presence of osteoporosis or phlebothrombosis.

Patients receiving SYMMETREL who note central nervous system effects or blurring of vision should be cautioned against driving or working in situations where alertness is important.

PRECAUTIONS: SYMMETREL (amantadine hydrochloride) should not be discontinued abruptly since a few patients with Parkinson's disease experienced a parkinsonian crisis, i.e., a sudden marked clinical deterioration, when this medication was suddenly stopped. The dose of anticholinergic drugs or of SYMMETREL should be reduced if atropine-like effects appear when these drugs are used concurrently.

The dose of SYMMETREL may need careful adjustment in patients with renal impairment, congestive heart failure, peripheral edema, or orthostatic hypotension. Since SYMMETREL is not metabolized and is mainly excreted in the urine, it may accumulate when renal function is inadequate.

Care should be exercised when administering SYMMETREL to patients with liver disease, a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents. Careful observation is required when SYMMETREL is administered concurrently with central nervous system stimulants.

No long-term studies in animals have been performed to evaluate the carcinogenic potential of SYMMETREL. The mutagenic potential of the drug has not yet been determined in experimental systems.

Pregnancy Category C: SYMMETREL (amantadine hydrochloride) has been shown to be embryotoxic and teratogenic in rats at 50 mg/kg/day, about 12 times the recommended human dose, but not at 37 mg/kg/day. Embryotoxic and teratogenic drug effects were not seen in rabbits which received up to 25 times the recommended human dose. There are no adequate and well-controlled studies in pregnant women.

SYMMETREL should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or the fetus.

Nursing Mothers: SYMMETREL is excreted in human milk. Caution should be exercised when SYMMETREL is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SYMMETREL in newborn infants, and infants below the age of 1 year have not been established.

ADVERSE REACTIONS: The most frequently occurring serious adverse reactions are: depression, congestive heart failure, orthostatic hypotensive episodes, psychosis, and urinary retention. Rarely convulsions, leukopenia, and neutropenia have been reported.

Other adverse reactions of a less serious nature which have been observed are the following: hallucinations, confusion, anxiety; irritability; anorexia, nausea, and constipation; ataxia and dizziness (lightheadedness); livedo reticularis and peripheral edema. Adverse reactions observed less frequently are the following: vomiting; dry mouth; headache; dyspnea; fatigue, insomnia, and a sense of weakness. Infrequently, skin rash, slurred speech, and visual disturbances have been observed. Rarely eczematoid dermatitis and oculogyric episodes have been reported.

DOSAGE AND ADMINISTRATION: Adult Dosage for Parkinsonism: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day when used alone. SYMMETREL has an onset of action usually within 48 hours.

The initial dose of SYMMETREL is 100 mg daily for patients with serious associated medical illnesses or who are receiving high doses of other antiparkinson drugs. After one to several weeks at 100 mg once daily, the dose may be increased to 100 mg twice daily, if necessary.

Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 400 mg daily in divided doses. However, such patients should be supervised closely by their physicians.

Patients initially deriving benefit from SYMMETREL not uncommonly experience a fall-off of effectiveness after a few months. Benefit may be regained by increasing the dose to 300 mg daily. Alternatively, temporary discontinuation of SYMMETREL for several weeks, followed by reinitiation of the drug, may result in regaining benefit in some patients. A decision to use other antiparkinson drugs may be necessary.

Dosage for Concomitant Therapy: Some patients who do not respond to anticholinergic antiparkinson drugs may respond to SYMMETREL. When SYMMETREL or anticholinergic antiparkinson drugs are each used with marginal benefit, concomitant use may produce additional benefit.

When SYMMETREL and levodopa are initiated concurrently, the patient can exhibit rapid therapeutic benefits. SYMMETREL should be held constant at 100 mg daily or twice daily while the daily dose of levodopa is gradually increased to optimal benefit.

When SYMMETREL is added to optimal well-tolerated doses of levodopa, additional benefit may result, including smoothing out the fluctuations in improvement which sometimes occur in patients on levodopa alone. Patients who require a reduction in their usual dose of levodopa because of the development of side effects may possibly regain lost benefit with the addition of SYMMETREL.

Dosage for Drug-Induced Extrapyramidal Reactions: Adult: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day. Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 300 mg daily in divided doses. 6043-15BSP/Rev. Oct. 1984

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REFERENCE: 1. Borison RL, Diamond BI: Treatment of extrapyramidal side-effects: Amantadine versus benztropine. *World J Psychosynthesis* (special), 1984-1985, pp 40-43.

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See important information on following page

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Only Ativan offers all these benefits...

rapid relief of anxiety

clearance not significantly delayed by age, liver or kidney dysfunction

cumulative sedative effects seldom a problem (Sedation, reported in 15.9% of patients in clinical trials, was generally mild and transitory.)

little likelihood of drug interaction (All benzodiazepines produce additive sedative effects when taken with alcohol or other CNS depressants.)

no significant changes in vital signs in cardiovascular patients*

short duration of action, simple metabolism

*Benzodiazepines have not been shown to be of benefit in treating the cardiovascular component.

Ativan®
(lorazepam) ℞

Specify Ativan—and assure your patients' therapy

Indicate one of the following on your prescriptions, as appropriate to your state laws:

- Do not substitute
- Brand necessary
- Dispense as written
- May not substitute
- Medically necessary
- No substitution
- NDPS (no drug product selection)

Brief Summary of Prescribing Information.

Indications and Usage: Management of anxiety disorders or short-term symptoms of anxiety or anxiety associated with depressive symptoms. An tension associated with stress of everyday life usually does not require trea with an anxiolytic.

Effectiveness in long-term use, i.e., more than 4 months, has not been a by systematic clinical studies. Reassess periodically usefulness of the dru individual patient.

Contraindications: Known sensitivity to benzodiazepines or acute narro glaucoma.

Warnings: Not recommended in primary depressive disorders or psycho As with all CNS-acting drugs, warn patients not to operate machinery or m vehicles, and of diminished tolerance for alcohol and other CNS depressa

Physical and Psychological Dependence: Withdrawal symptoms like th noted with barbiturates and alcohol have occurred following abrupt discor ance of benzodiazepines (including convulsions, tremor, abdominal and m cramps, vomiting and sweating). Addiction-prone individuals, e.g. drug a and alcoholics, should be under careful surveillance when on benzodiaze because of their predisposition to habituation and dependence. Withdraw symptoms have also been reported following abrupt discontinuance of be diazepines taken continuously at therapeutic levels for several months.

Precautions: In depression accompanying anxiety, consider possibility f suicide.

For elderly or debilitated patients, initial daily dosage should not exceed avoid oversedation. Terminate dosage gradually since abrupt withdrawal antianxiety agent may result in symptoms like those being treated: anxiety, tion, irritability, tension, insomnia and occasional convulsions. Observe us precautions with impaired renal or hepatic function. Where gastrointestinal diovascular disorders coexist with anxiety, note that lorazepam has not be shown of significant benefit in treating gastrointestinal or cardiovascular co nent. Esophageal dilation occurred in rats treated with lorazepam for more 1 year at 6mg/kg/day. No effect dose was 1.25mg/kg/day (about 6 times m mum human therapeutic dose of 10mg/day). Effect was reversible only wh ment was withdrawn within 2 months of first observation. Clinical significar unknown; but use of lorazepam for prolonged periods and in geriatrics rec caution and frequent monitoring for symptoms of upper G.I. disease. Safet effectiveness in children under 12 years have not been established.

ESSENTIAL LABORATORY TESTS: Some patients have developed leukop some have had elevations of LDH. As with other benzodiazepines, periodic counts and liver function tests are recommended during long-term therapy.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: Benzodiazepines proc CNS depressant effects when administered with such medications as barb or alcohol.

CARCINOGENESIS AND MUTAGENESIS: No evidence of carcinogenic po emerged in rats during an 18-month study. No studies regarding mutagene have been performed.

PREGNANCY: Reproductive studies were performed in mice, rats, and 2 st rabbits. Occasional anomalies (reduction of tarsals, tibia, metatarsals, mal limbs, gastroschisis, malformed skull and microphthalmia) were seen in dr treated rabbits without relationship to dosage. Although all these anomalie not present in the concurrent control group, they have been reported to occ randomly in historical controls. At 40mg/kg and higher, there was evidence resorption and increased fetal loss in rabbits which was not seen at lower d Clinical significance of these findings is not known. However, increased risk congenital malformations associated with use of minor tranquilizers (chlorc poxide, diazepam and meprobamate) during first trimester of pregnancy h been suggested in several studies. Because use of these drugs is rarely a of urgency, use of lorazepam during this period should almost always be av Possibility that a woman of child-bearing potential may be pregnant at instit therapy should be considered. Advise patients if they become pregnant to municate with their physician about desirability of discontinuing the drug. I humans, blood levels from umbilical cord blood indicate placental transfer lorazepam and its glucuronide.

NURSING MOTHERS: It is not known if oral lorazepam is excreted in humar like other benzodiazepines. As a general rule, nursing should not be under while on a drug since many drugs are excreted in milk.

Adverse Reactions, if they occur, are usually observed at beginning of the and generally disappear on continued medication or on decreasing dose. I sample of about 3,500 anxious patients, most frequent adverse reaction is s tion (15.9%), followed by dizziness (6.9%), weakness (4.2%) and unsteadin (3.4%). Less frequent are disorientation, depression, nausea, change in ap headache, sleep disturbance, agitation, dermatological symptoms, eye fun disturbance, various gastrointestinal symptoms and autonomic manifestati Incidence of sedation and unsteadiness increased with age. Small decreas blood pressure have been noted but are not clinically significant, probably t related to relief of anxiety.

Transient amnesia or memory impairment has been reported in associatic the use of benzodiazepines.

Overdosage: In management of overdosage with any drug, bear in mind m agents may have been taken. Manifestations of overdosage include somno confusion and coma. Induce vomiting and/or undertake gastric lavage follo general supportive care, monitoring vital signs and close observation. Hypc sion, though unlikely, usually may be controlled with Levarterenol Bitartrate Injection U.S.P. Usefulness of dialysis has not been determined.

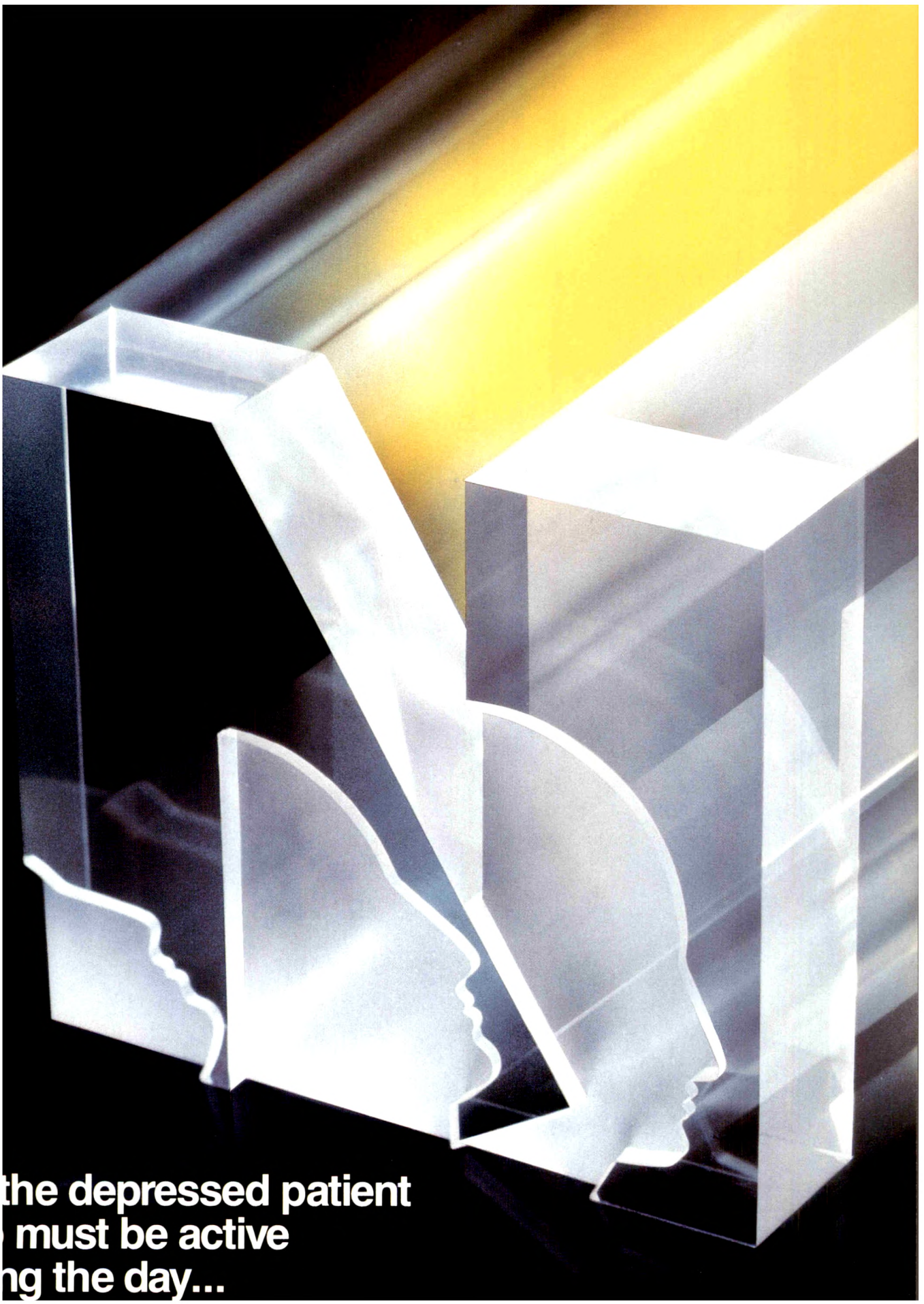


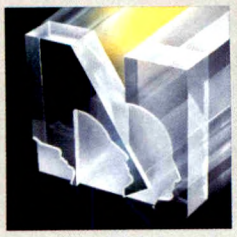
DOSAGE: Individualize for maximum beneficial effects. Inc dose gradually when needed, giving higher evening do before increasing daytime doses. Anxiety, usually 2-3 day given b.i.d. or t.i.d.; dosage may vary from 1 to 10 day in divided doses. For elderly or debilitated, initial 1-2mg/day; insomnia due to anxiety or transient situa stress, 2-4mg h.s.

HOW SUPPLIED: 0.5, 1.0 and 2.0mg tablets.

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Wyeth Labo
Philadel


the depressed patient
must be active
ng the day...



Norpramin®

(desipramine hydrochloride tablets USP

10, 25, 50, 75, 100, 150 mg

The fastest growing antidepressant in the U.S.A.

Now after 20 years, the antidepressant most widely prescribed by psychiatrist

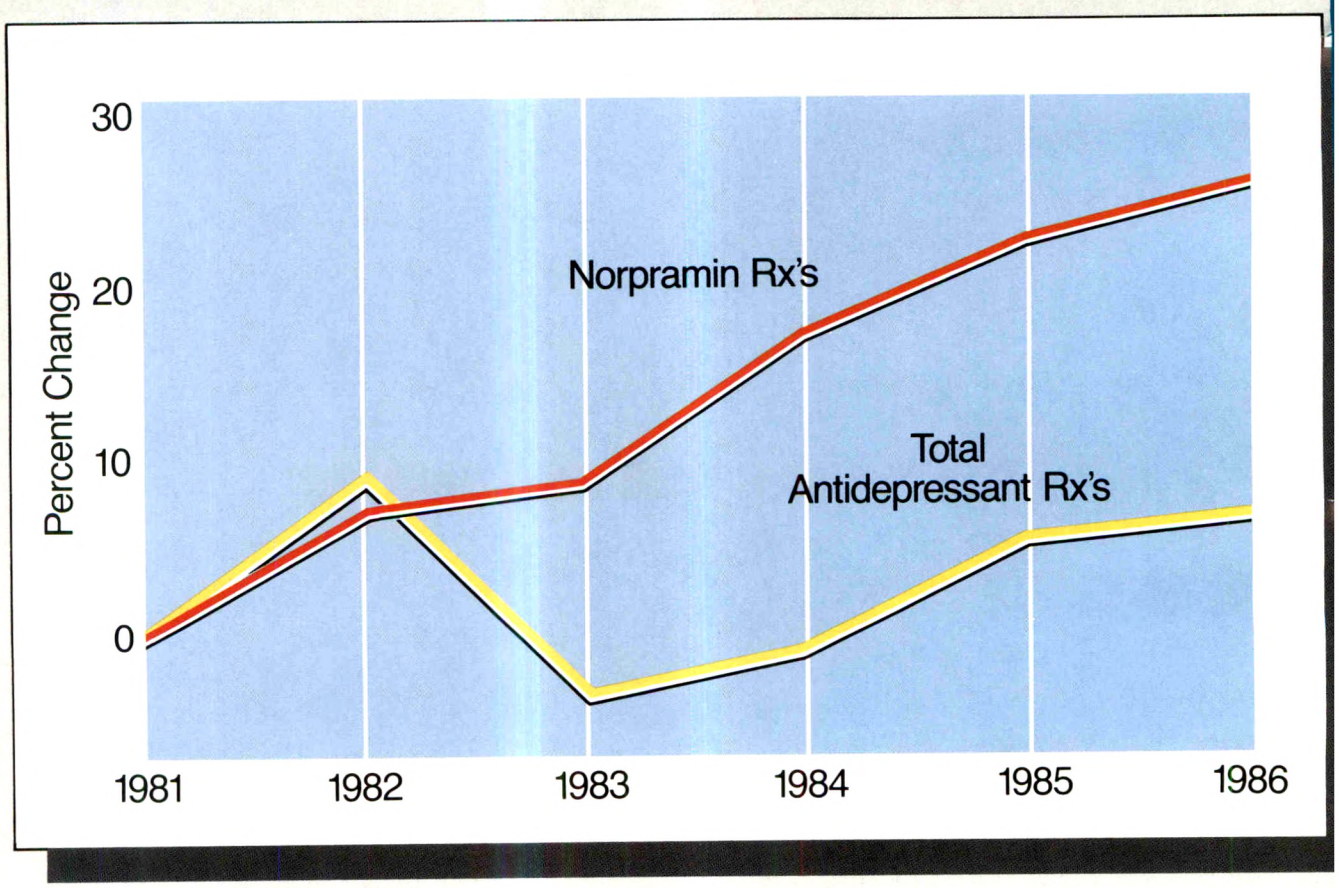


Figure 1.

The red line tracks the percent change in Norpramin prescriptions; the yellow line represents the percent change in total prescription activity the antidepressant market (based on IMS International *National Prescription Audit*, June 1986).

Merrell Dow

When a precise dosage titration and the added flexibility of once daily, single tablet dosing are desirable

"...selection of pharmacological agents that can be prescribed once or twice a day will improve patient compliance."[1]

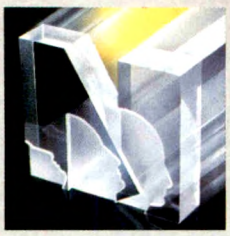
Norpramin allows you to choose

This		or	This	
25 mg tid			75 mg qd	
25 mg qid			100 mg qd	
50 mg tid			150 mg qd	

- the fastest growing antidepressant in the U.S.A.
- a 20-year record of efficacy in relieving the symptoms of depression
- a clinical profile well defined over time
- the choice of a once or twice daily single tablet dosage, and the added flexibility of six different dosage strengths

Greenberg RN: Overview of patient compliance with medication dosing: A literature review. Clin Ther 6:592-599, 1984.

rief Summary of Prescribing Information appears on the next page.



Norpramin

(desipramine hydrochloride tablets USP

10, 25, 50, 75, 100, 150 mg

Dosage Flexibility

Convenient choice of six tablet strengths and once daily or divided dosage schedule allows titration to individual response.

10 mg 25 mg 50 mg 75 mg 100 mg 150 mg

The antidepressant most widely prescribed by psychiatrists

Norpramin®
(desipramine hydrochloride tablets USP)

AVAILABLE ONLY ON PRESCRIPTION

Brief Summary

MECHANISM OF ACTION: Available evidence suggests that many depressions have a biochemical basis in the form of a relative deficiency of neurotransmitters such as norepinephrine and serotonin. Norepinephrine deficiency may be associated with relatively low urinary 3-methoxy-4-hydroxyphenyl glycol (MHPG) levels, while serotonin deficiencies may be associated with low spinal fluid levels of 5-hydroxyindolacetic acid.

While the precise mechanism of action of the tricyclic antidepressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the reuptake of these substances from the synapse in the central nervous system.

Evidence indicates that the secondary amine tricyclic antidepressants, including Norpramin, may have greater activity in blocking the re-uptake of norepinephrine. Tertiary amine tricyclic antidepressants, such as amitriptyline, may have greater effect on serotonin re-uptake.

Norpramin (desipramine hydrochloride) is not a monoamine oxidase (MAO) inhibitor and does not act primarily as a central nervous system stimulant. It has been found in some studies to have a more rapid onset of action than imipramine. Earliest therapeutic effects may occasionally be seen in 2 to 5 days, but full treatment benefit usually requires 2 to 3 weeks to obtain.

INDICATIONS: Norpramin (desipramine hydrochloride) is indicated for relief of symptoms in various depressive syndromes, especially endogenous depression.

CONTRAINDICATIONS: Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS: 1. Extreme caution should be used when this drug is given in the following situations: a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction. b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug. c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias. d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold. **2.** This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds. **3.** USE IN PREGNANCY: Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive. **4.** USE IN CHILDREN: Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. **5.** The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. **6.** In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

PRECAUTIONS: 1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly. **2.** If serious adverse effects occur, dosage should be reduced or treatment should be altered. **3.** Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates. **4.** The drug may cause exacerbation of psychosis in schizophrenic patients. **5.** Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs. **6.** Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated. **7.** Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered. **8.** If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (*e.g.*, chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin. **9.** This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride. **10.** Both elevation and lowering of blood sugar levels have been reported. **11.** Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression. **12.** Norpramin 25, 50, 75, and 100 mg tablets contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS: Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke.

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention, delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male, breast enlargement a galactorrhea in the female; increased or decreased libido, imp tence, testicular swelling; elevation or depression of blood sug levels.

Other: jaundice (simulating obstructive), altered liver functio weight gain or loss; perspiration, flushing; urinary frequency, no turia; parotid swelling; drowsiness, dizziness, weakness a fatigue, headache; alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abru cessation of treatment after prolonged therapy may produce na sea, headache, and malaise.

DOSAGE AND ADMINISTRATION: Not recommended for use children. Lower dosages are recommended for elderly patien and adolescents. Lower dosages are also recommended for ou patients compared to hospitalized patients, who are closely supe vised. Dosage should be initiated at a low level and increase according to clinical response and any evidence of intolerance Following remission, maintenance medication may be required f a period of time and should be at the lowest dose that will mainta remission.

Usual Adult Dose: The usual adult dose is 100 to 200 mg per da In more severely ill patients, dosage may be further increase gradually to 300 mg/day if necessary. Dosages above 300 mg/da are not recommended.

Dosage should be initiated at a lower level and increase according to tolerance and clinical response.

Treatment of patients requiring as much as 300 mg shou generally be initiated in hospitals, where regular visits by t physician, skilled nursing care, and frequent electrocardiogram (ECG's) are available.

The best available evidence of impending toxicity from very hig doses of Norpramin is prolongation of the QRS or QT intervals o the ECG. Prolongation of the PR interval is also significant, bu less closely correlated with plasma levels. Clinical symptoms o intolerance, especially drowsiness, dizziness, and postural hypo tension, should also alert the physician to the need for reductio in dosage. Plasma desipramine measurement would constitut the optimal guide to dosage monitoring.

Initial therapy may be administered in divided doses or a singl daily dose.

Maintenance therapy may be given on a once-daily schedule fo patient convenience and compliance.

Adolescent and Geriatric Dose: The usual adolescent and geriatri dose is 25 to 100 mg daily.

Dosage should be initiated at a lower level and increase according to tolerance and clinical response to a usual maximum of 100 mg daily. In more severely ill patients, dosage may be further increased to 150 mg/day. Doses above 150 mg/day are no recommended in these age groups.

Initial therapy may be administered in divided doses or a singl daily dose.

Maintenance therapy may be given on a once-daily schedule fo patient convenience and compliance.

OVERDOSAGE: See prescribing information for a discussion symptoms and treatment of overdose.

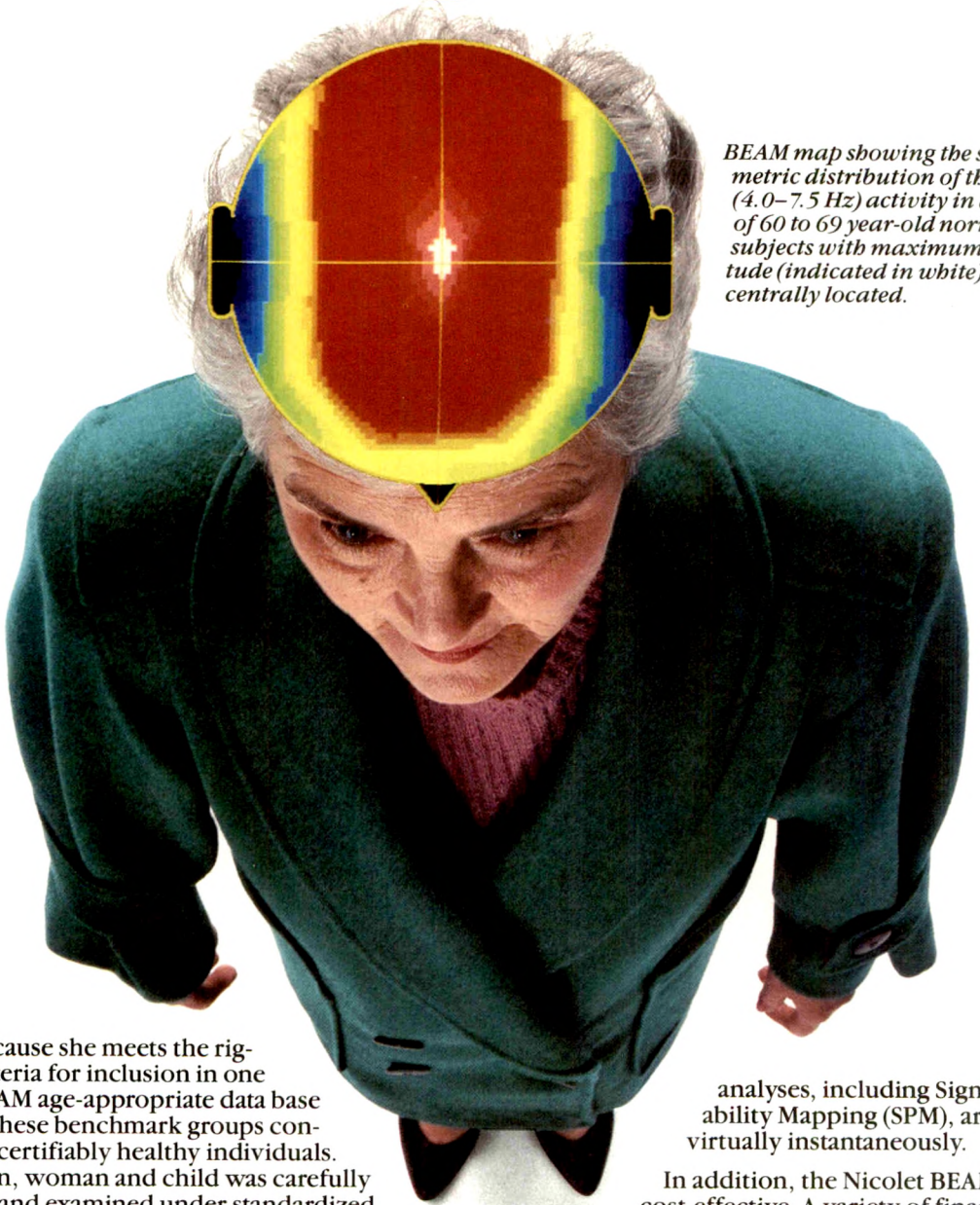
Product Information as of January, 1985.

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Electrophysiology

Books Received

The New Pediatric Guide to Drugs and Vitamins, by Edward R. Brace and Kenneth N. Anderson. Tucson, Ariz., Stonesong Press Book (Body Press), 1987, 282 pp., $7.95 (paper).

Sexuality and Mind: The Role of the Father and the Mother in the Psyche, by Janine Chasseguet-Smirgel. New York, New York University Press (Columbia University Press, distributor), 1986, 159 pp., $32.00.

The Brain Code: Mechanisms of Information Transfer and the Role of the Corpus Callosum, by Norman D. Cook. New York, Methuen, 1986, 254 pp., $35.00.

Drug Studies in the Elderly: Methodological Concerns, edited by Neal R. Cutler, M.D., and Prem K. Narang, Ph.D. New York, Plenum, 1986, 428 pp., $59.50.

The Psychologically Battered Child, by James Garbarino, Edna Guttmann, and Janis Wilson Seeley. San Francisco, Jossey-Bass, 1986, 272 pp., $24.95.

Pathology of Eating: Psychology and Treatment, by Sara Gilbert, B.A., M.Sc. New York, Routledge & Kegan Paul and Methuen, 1986, 234 pp., $35.00.

Dream Life, Wake Life: The Human Condition Through Dreams, by Gordon G. Globus. Albany, State University of New York Press, 1987, 196 pp., $34.50; $10.95 (paper).

The Good News About Depression: Cures and Treatments in the New Age of Psychiatry, by Mark S. Gold, M.D., New York, Villard Books, 1986, 328 pp., $18.95.

Bypass: A Cardiologist Reveals What Every Patient Needs to Know (1985), by Jonathan L. Halperin, M.D., and Richard Levine. Tucson, Ariz., Body Press, 1987, 284 pp., $8.95 (paper).

Developmental Therapy: Theory Into Practice, by Allen E. Ivey. San Francisco, Jossey-Bass, 1986, 370 pp., $27.95.

Lithium Encyclopedia for Clinical Practice, 2nd ed., by James W. Jefferson, M.D., John H. Greist, M.D., Deborah L. Ackerman, M.S., and Judith A. Carroll, B.A. Washington, D.C., American Psychiatric Press, 1987, 688 pp., $25.00 (spiral bound).

Notebooks of the Mind: Explorations of Thinking (1985), by Vera John-Steiner. New York, Perennial Library (Harper & Row), 1987, 251 pp., $8.95 (paper).

Maintaining Quality Under Pressure: The Dilemma of the Small Hospital. Special Publication of QRB: Quality Review Bulletin, Journal of Quality Assurance, edited by Paula S. Katz. Chicago, Joint Commission on Accreditation of Hospitals, 1986, 93 pp., $20.00 (paper).

The Nightmare: Psychological and Biological Foundations, edited by Henry Kellerman. New York, Columbia University Press, 1987, 363 pp., $40.00.

The Strangelove Legacy: Children, Parents, and Teachers in the Nuclear Age, by Phyllis La Farge. New York, Harper & Row, 1987, 242 pp., $15.95.

Guide for the Beginning Therapist: Relationship Between Diagnosis and Treatment, 2nd ed., by Amy Lamson, Ph.D. New York, Human Sciences Press, 1986, 125 pp., $19.95; $9.95 (paper).

Philosophy and Medicine, revised ed., by E.K. Ledermann, M.D., F.R.C.Psych. Brookfield, Vt., Gower Publishing Co., 1986, 170 pp., $41.50.

Techniques of Working With Resistance, edited by Donald S. Milman, Ph.D., and George D. Goldman, Ph.D. Northvale, N.J., Jason Aronson, 1987, 403 pp., $37.50.

The Impact of Illness on World Leaders, by Bert Edward Park, M.D. Philadelphia, University of Pennsylvania Press, 1986, 353 pp., $24.95.

A Leg to Stand On (1984), by Oliver Sacks. New York, Harper & Row, 1987, 222 pp., $7.95 (paper).

The Man Who Mistook His Wife for a Hat and Other Clinical Tales (1985), by Oliver Sacks. New York, Harper & Row, 1987, 243 pp., $7.95 (paper).

Psychopharmacology and Food: British Association for Psychopharmacology Monograph 7, edited by Merton Sandler and Trevor Silverstone. New York, Oxford University Press, 1985, 185 pp., $52.50.

Intimate Partners: Patterns in Love and Marriage, by Maggie Scarf. New York, Random House, 1987, 409 pp., $18.95.

Rat Man, by Stuart Schneiderman. New York, New York University Press (Columbia University Press, distributor), 1986, 115 pp., $25.00.

Heal Thyself: The Health of Health Care Professionals, edited by Cynthia D. Scott, Ph.D., M.P.H., and Joann Hawk, Ph.D. New York, Brunner/Mazel, 1986, 295 pp., $35.00.

Meaning in Mid-Life Transitions, by Edmund Sherman. Albany, State University of New York Press, 1987, 260 pp., $44.50; $14.95 (paper).

Psychiatric Examination of Children, 4th ed., by James E. Simmons, M.D. Philadelphia, Lea & Febiger, 1987, 250 pp., $18.00 (paper).

The Hidden Child: The Linwood Method for Reaching the Autistic Child, by Jeanne Simons and Sabine Oishi, Ph.D. Kensington, Md., Woodbine House, 1987, 251 pp., $17.95 (paper).

Cross-Cultural Anxiety, vol. 3, edited by Charles D. Spielberger and Rogelio Diaz-Guerrero. New York, Hemisphere Publishing Corp., 1986, 158 pp., $39.95.

Contemporary Perspectives on Psychotherapy With Lesbians and Gay Men, edited by Terry S. Stein, M.D., and Carol J. Cohen, M.D., New York, Plenum, 1986, 263 pp., $29.50.

Family Practitioner's Guide to Treating Depressive Illness, by Joseph Talley, M.D. Chicago, Precept Press, 1987, 300 pp., $39.95.

Psychotherapy and the Interminable Patient, edited by Jerome A. Travers. New York, Haworth Press, 1986, 144 pp., $19.95.

Soft Neurological Signs, edited by David E. Tupper, Ph.D. Orlando, Fla., Grune & Stratton (Harcourt Brace Jovanovich), 1987, 388 pp., $37.50.

Flowers on Granite: One Woman's Odyssey Through Psychoanalysis, by Dörte von Drigalski, M.D.; translated by Anthea Bell and Marianne Loring. Berkeley, Calif., Creative Arts Book Co., 1986, 315 pp., $16.95.

The Coping Capacity: On the Nature of Being Normal (1984), by Avery D. Weisman, M.D. New York, Human Sciences Press, 1986, 162 pp., $12.95 (paper).

About Mourning: Support and Guidance for the Bereaved (1985), by Savine Gross Weizman, Ph.D., and Phyllis Kamm. New York, Human Sciences Press, 1987, 236 pp., $16.95 (paper).

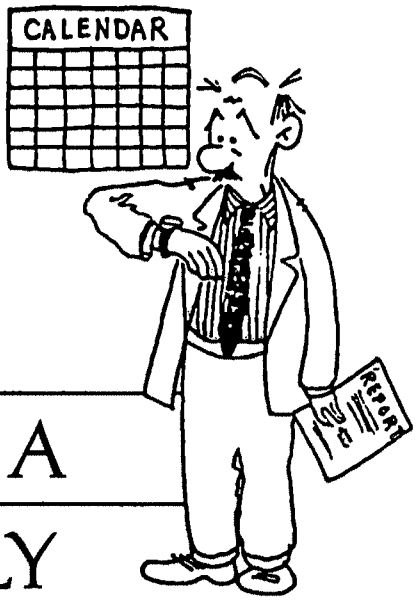
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The Myth of Neurosis: Overcoming the Illness Excuse, by Garth Wood. New York, Perennial Library (Harper & Row), 1986, 294 pp., $7.95 (paper).

Pain Management: Assessment and Treatment of Chronic and Acute Syndromes, edited by Wen-hsien Wu, M.D., M.S.; Leon G. Smith, M.D., consulting editor. New York, Human Sciences Press, 1987, 389 pp., $39.95.

The Natural History of Psychiatric Disorders in Children: A Study of Individuals Known to Have Attended Both Child and Adult Psychiatric Departments of the Same Hospital. Maudsley Monograph 29, by H. Zeitlin, B.Sc., M.Phil., M.D., M.R.C.P., F.R.C.Psych., New York, Oxford University Press, 1986, 152 pp., $39.95.

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Calendar

(Continued from page A00)

August 6–13, annual meeting, American Bar Association, San Francisco. Contact Thomas H. Gonser, Esq., Executive Director, 750 North Lake Shore Dr., Chicago, IL 60611; 312-988-5130.

August 9–13, annual meeting, American Institute of Biological Sciences, Columbus, Ohio. Contact Dr. Charles M. Chambers, Executive Director, 730 11th St., N.W., Washington, DC 20001-4584; 202-628-1500.

August 9–14, XIV Annual Symposium, Neuropsychiatric Aspects of Sociopathy, Kamuela, Hawaii. Contact Teresa Santana, S.C.N.P.I., 6794 La Jolla Blvd., La Jolla, CA 92037; 619-454-2102, 800-423-9521.

August 12–16, annual conference, American Association for Partial Hospitalization, Boston. Contact Joan Fridberg, 1221 Massachusetts Ave., N.W., Suite B, Washington, DC 20005; 202-347-1649.

August 17–21, annual meeting, American Sociological Association, Chicago. Contact Jen L. Suter, Meetings and Marketing Manager, ASA, 1722 N Street, N.W., Washington, DC 20036; 202-833-3410.

August 23–28, annual meeting, Canadian Medical Association, Charlottetown, Canada. Contact B.E. Freamo, Secretary-General, P.O. Box 8650, Ottawa, Ontario K1G 0G8, Canada; 613-731-9331.

August 28–September 1, annual meeting, American Psychological Association, New York. Contact Leonard D. Goodstein, Ph.D., Executive Officer, 1200 17th St., N.W., Washington, DC 20036; 202-955-7600.

August 30–September 1, annual meeting, International College of Psychosomatic Medicine, Sydney, Australia. Contact Professor Carins Aitken, M.D., Executive Director, Rehabilitation Studies Unit, Princess Margaret Rose Hospital, Edinburgh, EH10 7ED, Scotland.

SEPTEMBER

September 4–5, fall meeting, American Association for Social Psychiatry, New Orleans. Contact Carolyn B. Robinowitz, M.D., Secretary-Treasurer, AASP, 1400 K St., N.W., Washington, DC 20005; 202-682-6130.

September 9–12, annual meeting, National Association of Social Workers, New Orleans. Contact Mark G. Battle, A.C.S.W., Executive Director, 7981 Eastern Ave., Silver Spring, MD 20910; 301-565-0333.

September 11–13, annual conference, Canadian Art Therapy Association, Vancouver, Canada. Contact CATA, Conference Committee, 216 St. Clair Avenue West, Toronto, Ontario M4V 1R2, Canada; 416-921-4374.

September 11–15, annual meeting, Royal College of Physicians and Surgeons of Canada, Winnipeg, Canada. Contact Dr. J.H. Darragh, Executive Director, 74 Stanley Ave., Ottawa, Ontario K1M 1P4, Canada; 613-746-8177.

September 13–15, annual meeting, Canadian Academy of Child Psychiatry, London, Ontario. Contact J.H. Beitchman, M.D., Program Chairman, CACP, Clarke Institute of Psychiatry, 250 College St., Toronto, Ontario M5T 1R8, Canada.

September 14–17, annual meeting, American Academy of Family Physicians, San Francisco. Contact Robert Graham, M.D., Executive Vice-President, 1740 West 92nd St., Kansas City, MO 64114; 816-333-9700.

September 16–18, annual meeting, Canadian Psychiatric Association, London, Ontario. Contact Lea C. Metivier, Chief Administrative Officer, 225 Lisgar St., Suite 103, Ottawa, Ontario K2P 0C6, Canada; 613-234-2815.

September 17–18, semiannual meeting, American Board of Medical Specialties, Chicago. Contact Donald G. Langsley, M.D., Executive Vice-President, One American Plaza, Suite 805, Evanston, IL 60201; 312-491-9091.

September 18–20, child psychiatry examination, American Board of Psychiatry and Neurology, Minneapolis. Contact Stephen C. Scheiber, M.D., Executive Secretary, One American Plaza, Suite 808, Evanston, IL 60201; 312-846-0830.

September 22–25, International Symposium, Brain Acetylcholine: From Preclinical to Clinical Investigations, Taormina, Italy. Contact A.P. Caputi, M.D., Institute of Pharmacology, University of Messina, Piazza XX Settembre, 4, 98100 MESSINA (Italy); 090-712533.

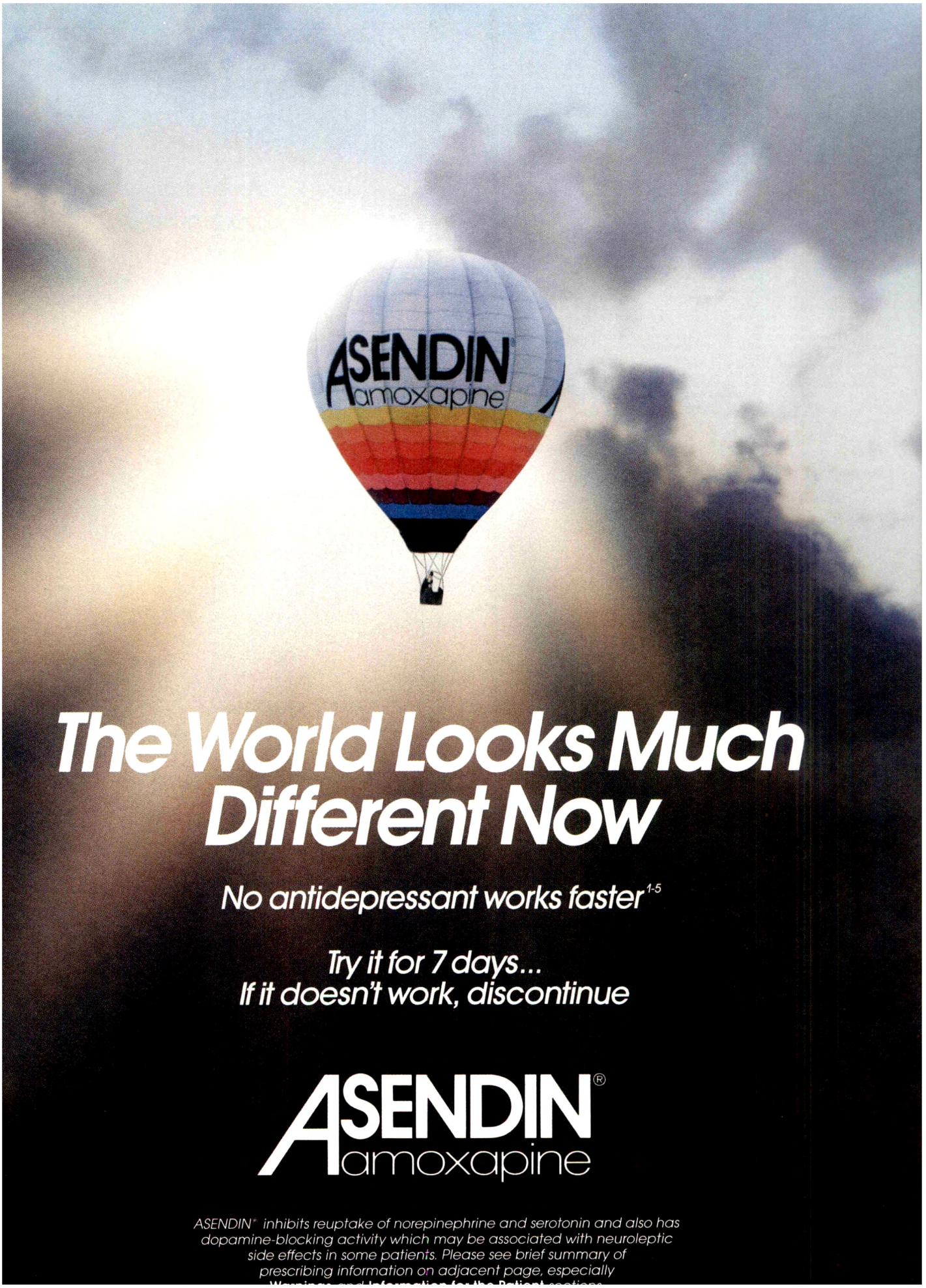
September 22–27, VIIIth European Congress of Child and Adolescent Psychiatry, Varna, Bulgaria. Contact Prof. Dr. Chr. Christosov, Dept. of Psychiatry, Medical Academy, Sofia, 1431, Bulgaria.

September 26–29, annual meeting, Southern Psychiatric Association, Boca Raton, Fla. Contact Annette S. Boutwell, Executive Director, P.O. Box 10387, Raleigh, NC 27605; 919-821-2226.

September 27–30, annual meeting, Association of Mental Health Administrators, Hollywood, Fla. Contact Weir Richard Kirk, Executive Director, 840 North Lake Shore Dr., Suite 1103W, Chicago, IL 60611; 312-943-2751.

September 27–October 2, annual meeting, American Health Care Association, New York. Contact Paul R. Willging, Ph.D., Executive Director, 1200 15th St., N.W., 8th Fl., Washington, DC 20005-2899; 202-833-2050.

September 28–October 3, annual meeting, Pan American Health Organization, Washington, D.C. Contact Carlyle Guerra de Macedo, M.D., Director, 525 23rd St., N.W., Washington, DC 20037; 202-861-3200.



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ASENDIN is absorbed rapidly and reaches peak blood levels approximately 90 minutes after ingestion. It is almost completely metabolized. The main route of excretion is the kidney. In vitro tests show that amoxapine binding to human serum is approximately 90%. In man, amoxapine serum concentration declines with a half-life of eight hours. However, the major metabolite, 8-hydroxyamoxapine, has a biologic half-life of 30 hours. Metabolites are excreted in the urine in conjugated form as glucuronides.

Clinical studies have demonstrated that ASENDIN has a more rapid onset of action than either amitriptyline or imipramine. The initial clinical effect may occur within four to seven days and occurs within 2 weeks in over 80% of responders.

INDICATIONS: *ASENDIN is indicated for relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions and depression accompanied by anxiety or agitation.*

CONTRAINDICATIONS: *Prior hypersensitivity to dibenzoxazepine compounds and in the acute recovery phase following myocardial infarction. Do not give concomitantly with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and monoamine oxidase inhibitors simultaneously. Before replacing a monoamine oxidase inhibitor with ASENDIN® amoxapine, allow a minimum of 14 days to elapse, then initiate cautiously, with gradual increase in dosage until optimum response is achieved.*

WARNINGS: Tardive Dyskinesia: *Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (ie, antipsychotic) drugs. (Amoxapine is not an antipsychotic, but it has substantive neuroleptic activity.) Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.*

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for Patients and Adverse Reactions.)

Use with caution in patients with history of urinary retention, angle-closure glaucoma, or increased intraocular pressure. Watch patients with cardiovascular disorders closely. Tricyclic antidepressants, particularly in high doses, can induce sinus tachycardia, changes in conduction time, and arrhythmias. Myocardial infarction and stroke have been reported with drugs of this class. Take extreme caution in patients with history of convulsive disorders or those with overt or latent seizure disorders.

PRECAUTIONS: General: *Because of inherent suicide potential, dispense to severely depressed patients the smallest suitable amount of the drug. Manic depressive patients may experience a shift to the manic phase; schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have such symptoms exaggerated, requiring reduction of dosage or addition of a major tranquilizer to the therapeutic regimen. Antidepressant drugs can cause skin rashes and/or "drug fever" in susceptible individuals. These allergic reactions may, in rare cases, be severe. They are more likely to occur during the first few days of treatment, but may also occur later. ASENDIN® amoxapine should be discontinued if rash and/or fever develop. Amoxapine possesses a degree of dopamine-blocking activity which may cause extrapyramidal symptoms in < 1% of patients. Rarely, symptoms indicative of tardive dyskinesia have been reported.* Information for the patient: *It is advised that all patients in whom chronic use of neuroleptic drugs is contemplated be given full information about the risk of tardive dyskinesia. Warn patients of possibility of drowsiness; performance of potentially hazardous tasks such as driving an automobile or operating machinery may be impaired.* Drug Interactions: *See Contraindications regarding concurrent usage of tricyclic antidepressants and monoamine oxidase inhibitors. Paralytic ileus may occur when tricyclic antidepressants are taken in combination with anticholinergic drugs. ASENDIN may enhance response to alcohol and the effects of barbiturates and other CNS depressants. Serum levels of several tricyclic antidepressants have been reported to be significantly increased when cimetidine is administered concurrently. Although such an interaction has not been reported to date with ASENDIN, specific interaction studies have not been done, and the possibility should be considered.* Therapeutic interactions: *Concurrent administration with electroshock may increase hazards associated with such therapy.* Carcinogenesis, Impairment of fertility: *In a 21-month toxicity study at three-dose levels in rats, pancreatic islet cell hyperplasia occurred with slightly increased incidence at doses 5-10 times the human dose. Pancreatic adenocarcinoma was detected in low incidence in the mid-dose group only, and may possibly have resulted from endocrine-mediated organ hyperfunction. The significance of these findings to man is not known. Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle length.* Pregnancy. Pregnancy Category C: *Studies performed in mice, rats, and rabbits have demonstrated no evidence of teratogenic effect due to ASENDIN. Embryotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetotoxic effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3-10 times the human dose. Decreased postnatal survival (between days 0-4) was demonstrated in the offspring of rats at 5-10 times the human dose. There are no adequate and well-controlled studies of pregnant women. ASENDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.* Nursing mothers: *ASENDIN, like many other systemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when ASENDIN is administered to nursing women.* Pediatric use: *Safety and effectiveness in children below the age of 16 have not been established.*

ADVERSE REACTIONS: *Reported in Controlled Studies:* Incidence greater than 1%—*Most frequent were sedative and anticholinergic—drowsiness (14%), dry mouth (14%), constipation (12%), and blurred vision (7%).*

Less frequently reported reactions were: CNS and Neuromuscular—*anxiety, insomnia, restlessness, nervousness, palpitations, tremors, confusion, excitement, nightmares, ataxia, alterations in EEG patterns.* Allergic—*edema, skin rash.* Endocrine—*elevation of prolactin levels.* Gastrointestinal—*nausea.* Other—*dizziness, headache, fatigue, weakness, excessive appetite, increased perspiration.* Incidence less than 1%—Anticholinergic—*disturbances of accommodation, mydriasis, delayed micturition, urinary retention, nasal stuffiness.* Cardiovascular—*hypotension, hypertension, syncope, tachycardia.* Allergic—*drug fever, urticaria, photosensitization, pruritus, rarely, vasculitis, hepatitis.* CNS and Neuromuscular—*tingling, paresthesias of the extremities, tinnitus, disorientation, seizures, hypomania, numbness, incoordination, disturbed concentration, hyperthermia, extrapyramidal symptoms, including, rarely, tardive dyskinesia. Neuroleptic malignant syndrome has been reported.* Hematologic—*leukopenia, agranulocytosis.* Gastrointestinal—*epigastric distress, vomiting, flatulence, abdominal pain, peculiar taste, diarrhea.* Endocrine—*increased or decreased libido, impotence, menstrual irregularity, breast enlargement, and galactorrhea in the female, syndrome of inappropriate antidiuretic hormone secretion.* Other—*lacrimation, weight gain or loss, altered liver function.* Drug Relationship Unknown: *Reported rarely, but under circumstances where drug relationship was unknown:* Anticholinergic—*paralytic ileus.* Cardiovascular—*atrial arrhythmias (including atrial fibrillation), myocardial infarction, stroke, heart block.* CNS and Neuromuscular—*hallucinations.* Hematologic—*thrombocytopenia, eosinophilia, purpura, petechiae.* Gastrointestinal—*parotid swelling.* Endocrine—*change in blood glucose levels.* Other—*pancreatitis, hepatitis, jaundice, urinary frequency, testicular swelling, anorexia, alopecia.*

Additional Adverse Reactions Reported with Other Antidepressant Drugs: Anticholinergic—*sublingual adenitis, dilation of the urinary tract.* CNS and Neuromuscular—*delusions.* Gastrointestinal—*stomatitis, black tongue.* Endocrine—*gynecomastia.*

OVERDOSAGE: Signs and Symptoms

Toxic manifestations of ASENDIN® amoxapine overdosage differ significantly from those of other tricyclic antidepressants. Serious cardiovascular effects are seldom, if ever, observed. However, CNS effects—particularly grand mal convulsions—occur frequently, and treatment should be directed primarily toward prevention or control of seizures. Status epilepticus may develop and constitutes a neurologic emergency. Coma and acidosis are other serious complications of substantial ASENDIN overdosage in some cases. Renal failure may develop two to five days after toxic dosage, typically in those who have experienced multiple seizures.

Treatment

Treatment of ASENDIN overdosage should be symptomatic and supportive, but with special attention to prevention or control of seizures. Seizures may respond to standard anticonvulsive therapies, such as intravenous diazepam and/or phenytoin. The value of physostigmine appears less certain. Status epilepticus, should it develop, requires vigorous treatment such as that described by Delgado-Escueta, et al (N Engl J Med 1982; 306: 1337-1340).

Convulsions, when they occur, typically begin within 12 hours after ingestion. Prophylactic administration of anticonvulsant medication during this period may be of value. Treatment of renal failure, should it occur, is the same as that for non-drug-induced renal dysfunction. Serious cardiovascular effects are remarkably rare following ASENDIN overdosage, and the ECG typically remains within normal limits, except for sinus tachycardia. Hence, prolongation of the QRS interval beyond 100 milliseconds within the first 24 hours is not a useful guide to the severity of overdosage with this drug. Fatalities and, rarely, neurologic sequelae have resulted from prolonged status epilepticus in ASENDIN overdosage patients.

Rev. 12/85

REFERENCES: 1. Hekimian LJ, Friedhoff AJ, Deever E: A comparison of the onset of action and therapeutic efficacy of amoxapine and amitriptyline. *J Clin Psychiatry* 1978;39:633-637. 2. Data on file, Lederle Laboratories, Pearl River, NY. 3. Hekimian LJ, Weise CC, Friedhoff AJ: Onset of action of amoxapine and doxepin in outpatients with "mixed anxiety/depression." *J Clin Psychiatry* 1983;44:248-252. 4. Paprocki J, Bustamante LS, Barcala Peixoto MP, et al: A double-blind comparison of amoxapine and imipramine in depression. *A Folha Medica* 1977;74:199-210. 5. Fabre LF: The treatment of depression in outpatients: A controlled comparison of the onset of action of amoxapine and maprotiline. *J Clin Psychiatry* 1985;46:521-524.

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Historical Perspective on the Appropriate Length of Therapy
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Carl Rickels, MD
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Long-Term Therapy: The Issue of Drug Withdrawal
Malcolm Lader, MD, PhD
Professor of Clinical Pharmacology
Institute of Psychiatry
University of London
London, England

Tuesday, May 12

PSYCHOTROPIC THERAPY: THE ISSUE OF DRUG-INDUCED IMPAIRMENT

Moderator:
Mark J. Mills, JD, MD
Professor, Department of Psychiatry and Biobehavioral Sciences
Director, Program in Psychiatry and Law, Neuropsychiatric Institute
University of California
Los Angeles, California

The Potential Impact of Drug-Induced Impairment: Recent Epidemiologic Evidence
Gerry Oster, PhD
Vice President and Senior Economist
Policy Analysis Inc.
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Drug-Induced Impairment: Recent Clinical Findings
Alison M. Smiley, PhD
President
Human Factors North, Inc.
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Drug-Induced Impairment: Potential Legal Implications
Mark J. Mills, JD, MD

Wednesday, May 13

SUICIDE: RECOGNITION AND PREVENTION

Moderator:
J. John Mann, MD
Associate Professor of Psychiatry
Cornell University Medical College
New York, New York

Epidemiology of Suicide
Gerald L. Klerman, MD
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Cornell University Medical College
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Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree.

Warnings: The risk of developing potentially irreversible *tardive dyskinesia* is believed to increase as duration of treatment and total cumulative dose increase, although it is impossible to predict who will develop the syndrome. It can also develop, although much less commonly, after brief treatment with low doses. Incidence appears to be highest among the elderly, especially elderly women. Generally chronic treatment should be reserved for chronically ill patients whose disease is most likely to respond to neuroleptic drugs and for whom other effective, less harmful treatment is not available or appropriate. There is no known treatment for tardive dyskinesia although the syndrome may partially or completely remit upon withdrawal of neuroleptic treatment. If signs and symptoms of tardive dyskinesia appear, drug discontinuation should be considered. Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides; carefully consider benefit versus risk in less severe disorders. During pregnancy, administer only when the potential benefits exceed the possible risks to mother and fetus.

Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy, observed primarily in patients receiving larger than recommended doses, is characterized by diminution of visual acuity, brownish coloring of vision, and impairment of night vision; the possibility of its occurrence may be reduced by remaining within recommended dosage limits. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving), and increase dosage gradually. Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension since phenothiazines may induce a reversed epinephrine effect on occasion.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. Daily doses in excess of 300 mg should be used only in severe neuropsychiatric conditions.

Information for Patients: It is suggested that all patients who are candidates for chronic treatment be advised of the risk of tardive dyskinesia.

Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; rarely, nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—ECG changes (see *Cardiovascular Effects* below). *Other*—Rare cases described as parotid swelling.

It should be noted that efficacy, indications and untoward effects have varied with the different phenothiazines. It has been reported that old age lowers the tolerance for phenothiazines; the most common neurological side effects are parkinsonism and akathisia, and the risk of agranulocytosis and leukopenia increases. The following reactions have occurred with phenothiazines and should be considered whenever one of these drugs is used:

Autonomic Reactions—Miosis, obstipation, anorexia, paralytic ileus. *Cutaneous Reactions*—Erythema, exfoliative dermatitis, contact dermatitis. *Blood Dyscrasias*—Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia. *Allergic Reactions*—Fever, laryngeal edema, angioneurotic edema, asthma. *Hepatotoxicity*—Jaundice, biliary stasis. *Cardiovascular Effects*—Changes in the terminal portion of electrocardiogram including prolongation of Q-T interval, lowering and inversion of T-wave, and appearance of a wave tentatively identified as a bifid T or a U wave have been observed with phenothiazines, including Mellaril (thioridazine); these appear to be reversible and due to altered repolarization, not myocardial damage. While there is no evidence of a causal relationship between these changes and significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients showing characteristic electrocardiographic changes while taking the drug. While proposed, periodic electrocardiograms are not regarded as predictive. Hypotension, rarely resulting in cardiac arrest. *Extrapyramidal Symptoms*—Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonus, oculogyric crises, tremor, muscular rigidity, and akinesia. *Tardive Dyskinesia*—Characterized by involuntary choreoathetoid movements variously involving the tongue, face, mouth, lips or jaw (e.g., protrusion of the tongue, puffing of the cheeks, puckering of the mouth, chewing movements), trunk and extremities—may be recognized during treatment upon dosage reduction or withdrawal of treatment. Movements may decrease or disappear if further treatment is withheld, although this reversibility is more likely after short-term rather than long-term treatment. Since neuroleptics may mask the signs of tardive dyskinesia, reducing dosage periodically increases the likelihood of detecting the syndrome at the earliest possible time. *Endocrine Disturbances*—Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema, false positive pregnancy tests. *Urinary Disturbances*—Retention, incontinence. *Others*—Hyperpyrexia; behavioral effects suggestive of a paradoxical reaction, including excitement, bizarre dreams, aggravation of psychoses, and toxic confusional states; following long-term treatment, a peculiar skin-eye syndrome marked by progressive pigmentation of skin or conjunctiva and/or accompanied by discoloration of exposed sclera and cornea; stellate or irregular opacities of anterior lens and cornea; systemic lupus erythematosus-like syndrome.

Dosage: Dosage must be individualized according to the degree of mental and emotional disturbance, and the smallest effective dosage should be determined for each patient. [MEL-Z37—5/1/85]

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THE AMERICAN JOURNAL OF PSYCHIATRY

Schizoaffective Mania Reconsidered

Douglas F. Levinson, M.D., and Maria E.M. Levitt, B.A.

Schizoaffective mania refers to a heterogeneous group of disorders characterized by mixtures of schizophrenic and manic (or bipolar) symptoms. Of the proposed diagnostic criteria, the Research Diagnostic Criteria (RDC) most clearly distinguish relevant subgroups. Family, clinical, and treatment studies suggest that the RDC's mainly affective subtype of schizoaffective mania is a variant of psychotic bipolar disorder. Limited available data suggest that the mainly schizophrenic subtype has a poorer prognosis and includes cases more closely related to schizophrenia. Schizoaffective mania also overlaps with proposed categories such as reactive and cycloid psychosis. It is premature to assume that all schizoaffective manic disorder represents a bipolar variant. Further studies that differentiate patients according to subtype, drug response, and course are needed.

(Am J Psychiatry 1987; 144:415–425)

It has become clear over the last 15 years that in many settings a majority of patients with bipolar disorder have been misdiagnosed as schizophrenic (1, 2); this is particularly true of those with onset during adolescence or early adulthood, who tend to have more psychotic and bizarre symptoms (3, 4). It has also been recognized that while many bipolar patients have schizophrenia-like symptoms at times, it is a matter of some urgency to diagnose bipolar disorders correctly because of the obviously greater safety and (for bipolar patients) effectiveness of long-term lithium versus neuroleptic therapy. Awareness of these issues helped to stimulate the development of more specific, operationalized diagnostic criteria (5, 6, and *DSM-III*) and has led to a growing assumption that "schizoaffective" patients with manic or bipolar affective symptoms have severe forms of bipolar disorder (7, 8).

There are insufficient empirical data, however, to support such a sweeping conclusion about schizoaffective disorders. The Research Diagnostic Criteria (RDC) (6), for example, distinguish between mainly affective, mainly schizophrenic, and unclassifiable ("other") subtypes of schizoaffective mania on the basis of premorbid functioning and whether schizophrenia-like symptoms persist after remission of affective symptoms. While the clinical, familial, and pharmacologic evidence summarized in this paper suggests that the mainly affective subtype is a form of bipolar disorder, little is known about other subtypes.

Research in this area has been hampered not only by the use of varying diagnostic criteria but also by the reporting of combined data for several or all schizoaffective groups. For example, most investigators have analyzed mixed samples of schizoaffective patients with manic, bipolar, and depressed affective syndromes. The data we present here suggest that patients with schizoaffective mania are distinct from those with pure schizoaffective depression and that schizoaffective mania is itself a heterogeneous disorder whose subgroups remain poorly understood. To draw premature conclusions on this subject would only serve to obstruct needed research.

DEFINITIONS OF SCHIZOAFFECTIVE MANIA

Several operational definitions of schizoaffective mania have been proposed (6, 9–14); these are summarized in appendix 1. Vogl and Zaudig (15) found high agreement (71%–93%) among the RDC, Welner (10), and Kendell (11) criteria, although not between the

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The authors thank Jean Endicott, Ph.D., for discussion of issues presented in the article and Mrs. Julie Holub for preparation of the manuscript.

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RDC and *ICD* (47%), in a mixed group of schizoaffective manic and schizoaffective depressed patients. However, Brockington and Leff (16) found concordance of no more than .34 between any of these methods when they were applied to first-admission mixed schizoaffective patients, most of them depressed. Thus, large numbers of schizoaffective manic patients have not been studied using alternative diagnostic criteria. Studies may be identifying quite different groups of patients.

Few clinicians have been trained to use operational criteria for schizoaffective disorders. *DSM-III* offers no such criteria, although the *DSM-III Casebook* (17) provides examples to guide these diagnoses. Thus, diagnoses of schizoaffective mania in hospital and clinic records are generally based on a clinical impression of mania with more psychosis, thought disorder, or flatness than usual or of schizophrenia with more excitement than usual. Many such patients are actually schizophrenic or manic according to the RDC. We consider the RDC (although imperfect) to be preferable to other proposed systems because they draw upon the most accepted current definitions of the manic, depressive, and schizophrenic syndromes while permitting classification of patients along most of the relevant dimensions.

The RDC system provides specific criteria for schizoaffective disorders along several dimensions and is the most widely used for research purposes. Although the current state of knowledge in this area requires a rather complex set of subtypes, this fact may have impeded more widespread understanding of these criteria. The RDC for schizoaffective disorders are primarily cross-sectional (i.e., are applied to a specific acute episode). They require that a patient simultaneously have a full affective syndrome and one of a group of symptoms considered characteristic of schizophrenia. Subtyping is along two dimensions.

1. *Manic versus depressed.* The current affective component is defined by the usual criteria for depressive and manic episodes, familiar to clinicians.

2. *Mainly affective versus mainly schizophrenic.* These criteria are less familiar to most clinicians and deserve some emphasis. a) Patients with the mainly affective subtype only have their schizophrenia-like symptoms at the same time as their "prominent" mania or depression, and they lack schizophrenia-like poor premorbid features. This subtype corresponds to the *DSM-III* diagnosis of bipolar disorder with nonmood-congruent psychotic features and probably represents a variant of bipolar disorder. Patients with the mainly affective subtype tend to report a bipolar history of depressive and manic episodes if specific inquiry is made (Jean Endicott, Ph.D., personal communication, June 1985). b) Patients with the mainly schizophrenic subtype either show schizophrenia-like poor premorbid features or have schizophrenia-like symptoms persisting for at least a week after remission of affective symptoms. The current draft of *DSM-III-R* essentially adopts the RDC definition of the mainly schizophrenic subtype to define schizoaffective disorders, except that there is a requirement of 2 weeks (rather than 1 week) of persisting schizophrenic symptoms in the absence of prominent affective features. Some patients do not definitely fit either subtype and are given a diagnosis of schizoaffective mania, other; additional criteria are provided for acute, subacute, subchronic, and chronic presentations.

There are many criticisms of the RDC for schizoaffective disorders, among which three major types of questions stand out. Are the criteria for schizophrenia-like symptoms optimal? (a question that unfortunately cannot yet be answered for "pure" schizophrenic patients either). Should there be further subtyping based on long-term course, whether patients have schizoaffective features during every acute episode (or chronically), and whether their affective features are bipolar? Finally, it is difficult to apply criteria consistently to patients with different drug treatments; for example, if manic symptoms greatly diminish during therapy with lithium alone, should the continued presence of schizophrenia-like symptoms lead to the diagnosis of schizoaffective mania, mainly schizophrenic subtype? What of the opposite case, in which neuroleptics lessen psychosis but affective symptoms persist?

Maj and Perris (14) raised a number of these points while suggesting that RDC schizoaffective disorders are quite heterogeneous. They proposed a multiaxial set of schizoaffective criteria (appendix 1). Their criteria for manic versus depressed and for affective (episodic) and schizophrenic (continuous) dimensions are similar to the RDC (with Comprehensive Psychiatric Rating Scale [18] item definitions), but they have added one longitudinal dimension—whether affective and schizophrenic syndromes appear consecutively or concurrently—and one historical dimension—whether there are associated factors such as drug abuse or known organic illness. They did not specifically subtype for consistency or bipolarity of symptoms longitudinally, although they presented some data on this subject that we shall discuss later.

We conclude that the RDC continue to represent the best operational criteria for subtyping schizoaffective disorders along the manic-depressed and mainly affective-schizophrenic dimensions. For the mainly affective groups, the "schizo"-affective label is probably unwarranted, but the term "non-mood-congruent" is an awkward one. Future investigators should consider adding longitudinal/historical dimensions that may further clarify meaningful clinical groups, such as bipolar versus nonbipolar course and recurrent schizoaffective episodes versus both schizoaffective and nonschizoaffective episodes.

PREVALENCE

Studies of the prevalence of schizoaffective mania (7, 12, 13, 16, 19, 20) are summarized in table 1. Estimates range from 0.2% to 23.7% of hospital admis-

TABLE 1. Prevalence of Schizoaffective Disorder and Schizoaffective Mania Among Psychiatric Admissions in Several Studies

Authors	Criteria	Number of Admissions	Schizoaffective Disorder		Schizoaffective Mania	
			N	%	N	%
Brockington et al. (11)	RDC	About 3,800	—	—	8	0.2
Brockington and Leff (16)[a]	RDC	322	8	2.5	1	0.3
Croughan et al. (19)	Welner (10)	About 6,900	110	1.6	22	0.3
Abrams and Taylor (12)	Abrams and Taylor	247	—	—	10	4.0
Abrams and Taylor (20)	Abrams and Taylor	465	—	—	69	14.8
Pope et al. (7)	RDC	219	61	27.8	52	23.7
Levinson and Levitt (unpublished)	RDC	395	43	10.9	32	8.1
Himmelhoch et al. (13)	Himmelhoch et al.	542[b]	34	6.3	24	4.4

[a]First lifetime hospital admissions only.
[b]Outpatients referred to affective disorders clinic.

TABLE 2. Results of Four Family Studies of Schizoaffective Disorders

Probands' Diagnosis	Study	Number of Probands	First-Degree Relatives' Age-Corrected Morbid Risk (%)				
			Schizophrenia	Affective Disorder	Bipolar Disorder	Unipolar Major Depressive Disorder	Schizoaffective Disorder
Schizoaffective disorder (all subtypes)	Angst et al. (21)	150	5.3	6.7	1.1	5.6	3.0
	Mendlewicz et al. (22)	55	10.8	34.6	—	—	—
Schizoaffective disorder, mainly affective subtype	Angst et al.	73	4.6	7.8	—	—	2.9
	Baron et al. (24)	22	0	28.1	1.6	26.5	3.2
	Gershon et al. (23)	11	3.6	31.3	16.8	14.5	6.1
Bipolar disorder	Mendlewicz et al.	55	1.8	39.4	—	—	—
	Baron et al.	40	0.7	30.8	14.5	16.3	1.5
	Gershon et al.	96[a]	0.2	22.6	8.6	14.0	1.1
Schizoaffective disorder, mainly schizophrenic subtype	Angst et al.	72	5.9	5.8	—	—	3.3
	Baron et al.	28	4.1	10.9	0	10.9	1.4
Schizophrenia	Mendlewicz et al.	55	16.9	8.6	—	—	—
	Baron et al.	50	7.9	5.1	0.6	4.5	2.3

[a]Probands had bipolar I disorder.

sions. This variability may in part be due to real differences in the samples. Pope et al. (7) and Levinson and Levitt (unpublished data) studied consecutive admissions to wards with specialized research functions. Himmelhoch and associates (13) studied patients in an affective disorders clinic; the other studies were of consecutive admissions to academic hospitals. Nothing is known about the incidence or prevalence in chronic-care or community settings. Considering the schizophrenic subtype separately, Levinson and Levitt (unpublished data) made this diagnosis in 3.5% of 395 admissions over 2 years (they excluded known organic disorders and undiagnosed brief admissions); Himmelhoch et al. (13) identified 4.4% of their patients as meeting criteria resembling RDC schizoaffective mania, schizophrenic subtype. Although the true prevalence of schizoaffective mania and its subtypes in the population must be considered unknown at this time, they are not uncommon in some settings.

FAMILY STUDIES

The four family studies (21–24) of schizoaffective probands summarized in table 2 met strict methodological criteria, including direct structured interview with most first-degree relatives by raters blind to the proband's diagnosis. In each of these studies, either all the schizoaffective subjects were combined for analyses or both manic and depressed subjects were combined into mainly affective and mainly schizophrenic groups. Mainly schizophrenic subtype patients (probands) were never studied separately. Mainly affective subtype patients had high familial rates of affective disorder, as can be seen in the studies of Baron et al. (24) and of Gershon et al. (23) (who commented that nine of their 11 schizoaffective subjects were considered clinically to have affective disorders). On the basis of these data, both of these groups of investigators have proposed a "multiple threshold" model for affective disorders, in which unipolar, bipolar, and schizoaffective disorders represent increasingly severe disorders, with increasing familial vulnerability, along a single continuum of risk, rather than representing distinct, independent disorders. Gershon and associates' data could be fitted to such a model, but those of Baron et al. could not.

For the mainly schizophrenic subgroup, however, these conclusions may not be valid. Baron and associates' data (24) suggest that familial schizophrenia may

be more common in the RDC-diagnosed mainly schizophrenic subtype group, with affective disorder rates not elevated in these families, although Angst et al. (21), using different diagnostic criteria, found less difference between the affective and schizophrenic subtypes. Familial schizophrenia rates for schizoaffective patients are generally intermediate between those for schizophrenic and affective patients, suggesting that at least some of the excess may be due to relatives of patients of the mainly schizophrenic subtype.

Data from the recent National Institute of Mental Health (NIMH) Collaborative Program on the Psychobiology of Depression also suggest differences between affective and some schizoaffective disorders. The schizoaffective manic patients studied were almost entirely of the affective subtype, and, as expected, they had high familial rates of affective disorders (Jean Endicott, Ph.D., personal communication, June 1985). Relatives of schizoaffective depressed probands had higher rates of psychosis (12.7% had psychotic depression, schizoaffective depression, schizophrenia, or unspecified functional psychosis) than relatives of psychotic or nonpsychotic depressive patients; relatives of psychotic depressive patients had more psychotic depression and schizoaffective depression than did relatives of nonpsychotic patients (25). The investigators have suggested that some psychotic forms of affective and schizoaffective disorders may be genetically distinct from the nonpsychotic forms. The theory of increased severity of a common vulnerability was not supported for schizoaffective depression: relatives of schizoaffective depressed, psychotic, and nonpsychotic depressed patients had similar total rates of affective disorders. In support of these findings, Maj (26) also reported a high familial prevalence of schizophrenia, but not of affective disorders, for schizoaffective depressed patients.

Studies using family history data or direct interviews with a smaller proportion of relatives (7, 11, 12, 27, 28) have generally found an unusually low rate of schizophrenia in the relatives of both schizophrenic and schizoaffective patients, with a higher rate of affective disorder. The good prognosis reported for schizoaffective patients in several of these studies (7, 12, 20) suggests that most subjects were from the mainly affective subtype as defined by the RDC. Maj (26), on the other hand, studied schizoaffective manic patients, many of them with recurrent schizoaffective manic episodes. Compared with bipolar patients, the schizoaffective manic patients had a lower familial prevalence of affective disorder and greater prevalence of schizophrenia and schizoaffective disorder.

Are there genetically distinct forms of schizoaffective disorder? While higher rates of schizoaffective disorders were found in the relatives of schizoaffective patients in some of these studies, there were much higher familial rates of affective and/or schizophrenic disorders, leading most investigators to conclude that schizoaffective disorders in general do not represent a distinct form of psychosis. Individual families have been reported to have multiple schizoaffective disorders (29, 30). Welner and Fishman (31) reported that most psychotic relatives of schizoaffective patients had both schizophrenia-like and affective symptoms, but only relatives with known psychotic histories were directly studied, no comparison group was studied, and schizoaffective mania was not considered separately from schizoaffective depression. Cohen et al. (32), reviewing Veterans Administration records, found a higher concordance among monozygotic twins for schizoaffective than for bipolar or schizophrenic disorder, but standardized diagnostic criteria were not used, and the same person reviewed the records of both twins. Tsuang (33) found fewer psychotic twin pairs concordant for schizoaffective disorders than were expected; most often the other sibling had an affective or schizophrenic disorder.

On the basis of family studies, then, schizoaffective mania of the mainly affective subtype may be closely related to bipolar disorder or a more psychotic variant of it, while the mainly schizophrenic subtype has not been separately studied. At least some schizophrenic subtype disorders may be familially related to schizophrenia. It is unclear whether there is a group of schizoaffective manic patients who have a distinct disorder.

CLINICAL FEATURES AND COURSE OF ILLNESS

Like the family studies, clinical and follow-up studies have tended to lump schizoaffective mania and schizoaffective depression together for data analysis and/or to combine the affective and schizophrenic subtypes of schizoaffective mania. Table 3 summarizes nine follow-up studies (7, 8, 11–13, 20, 26, 34, 35) in which schizoaffective manic patients were specifically noted to make up all or most of one of the groups.

In one group of studies (7, 8, 12, 20, 34), schizophrenia-like symptoms were not found to predict other clinical variables or outcome of manic patients. With one exception (7), these studies included a selection bias for patients meeting narrow criteria for mania, with subsequent identification of patients with schizophrenia-like symptoms. It is likely that most patients in this group of studies would have been given a diagnosis of schizoaffective mania, mainly affective subtype, by the RDC.

A second group of studies found less favorable outcomes. Brockington et al. (11) found only eight patients who met the RDC for schizoaffective mania among 32 with "schizomanic" symptoms, and this group had schizophrenia-like outcomes. Himmelhoch et al. (13) studied only patients with chronic thought disorder, so that all of their subjects would be schizoaffective, schizophrenic subtype, according to the RDC, and two-thirds thus had schizoaffective mania, schizophrenic subtype; they had impressively poor outcomes. Maj (26) found only nonsignificantly worse outcome for schizoaffective manic than for bipolar patients, but schizoaffective manic patients without

TABLE 3. Results of Nine Follow-Up and Clinical Studies of Schizoaffective Disorders

Authors	Subjects	Schizoaffective Disorder Criteria	Global Outcome: Length of Follow-Up	Global Outcome: Schizoaffective Mania Versus Bipolar or Affective Disorder	Global Outcome: Schizoaffective Mania Versus Schizophrenia	Other Findings
Studies of outcome						
Brockington et al. (11)	32 schizomanic (RDC: 8 schizoaffective mania, 8 schizophrenic, 16 bipolar)	Authors' and RDC	3.8 years	Worse	Worse	Hallucinations or passivity delusions predicted poor outcome
Pope et al. (7)	52 schizoaffective mania; 34 bipolar; 41 schizophrenic	RDC	1.5–5 years	Same	Better	
Rosenthal et al. (8)	71 bipolar I (46 bipolar, 25 schizoaffective mania)	RDC (excluded chronic psychosis)	6 months	Same		
Grossman et al. (35)	39 schizoaffective (15 schizoaffective mania, 24 schizoaffective depressed; 11 schizoaffective, schizophrenic subtype, 24 schizoaffective, affective subtype, 4 schizoaffective, other); 47 schizophrenic; 33 bipolar; 48 unipolar major depressive disorder	RDC	15.5 months	Worse	Same	10% of schizoaffective subjects had good outcome; schizoaffective mania was the same as schizoaffective depression and affective subtype was the same as schizophrenic subtype on global outcome
Maj (26)	17 schizoaffective mania; 16 bipolar	RDC	3 years	Same	Same	Recurrent schizoaffective mania common
Studies of clinical variables						
Abrams and Taylor (20)	78 bipolar; 10 bipolar (with Schneiderian first-rank symptoms)	Abrams and Taylor				No difference on outcome and therapy measures
Abrams and Taylor (12)	111 mania (69 with more than one schizophrenic symptom)	Feighner and RDC				No difference on family history, clinical, laboratory, or demographic measures
Himmelhoch et al. (13)	39 schizoaffective (24 schizophrenic subtype)	RDC plus chronic thought disorder				44% deteriorated; 55% had little or no therapeutic response
Pi and Surawicz (34)	39 bipolar (12 with Schneiderian first-rank symptoms)	Abrams and Taylor				No other clinical or therapeutic differences for those with and without Schneiderian first-rank symptoms

depressive episodes (i.e., without a bipolar course) showed a worse outcome. Grossman et al. (35) also found relatively poor outcomes for schizoaffective patients. This was the only study to examine outcome differences for schizoaffective mania versus schizoaffective depression and the schizoaffective, affective subtype, versus the schizophrenic subtype; no differences were found. However, with only 15 schizoaffective manic subjects and only 28% of the schizoaffective subjects from the schizophrenic subgroup, it can be inferred that an insufficient number of schizophrenic subgroup subjects were studied.

The three major studies of pooled schizoaffective subjects (9, 36, 37) generally found a high rate of chronic illness in schizoaffective patients and an overall outcome intermediate between those of bipolar and schizophrenic patients, but the outcome of schizoaffective mania was not described.

There has been little study of the consistency of the schizoaffective mania syndrome over time. Maj's (26) schizoaffective manic patients were about equally divided between those with a past history of depressed or schizoaffective depressed episodes and those with recurrent schizoaffective manic episodes only (who, as we have noted, had a poorer outcome). Prospectively, of 17 schizoaffective manic patients studied over a 3-year period, four (24%) had a bipolar course without reappearance of schizophrenia-like features and six (35%) had further schizoaffective manic episodes only. We too have seen a number of patients with

recurrent or chronic presentations of schizoaffective mania. More data are needed concerning consistency of diagnosis in relation to treatment response and outcome measures.

It appears, then, that there are (at least in some clinical settings) considerable numbers of patients with manic, usually bipolar, illness who also have schizophrenia-like symptoms during acute episodes but who may not have worse outcomes, at least over a period of several years. However, insufficient numbers of patients specifically identified as having schizoaffective mania of the affective or schizophrenic subtype (or other meaningful categories) have been selected from diverse clinical populations and studied long-term. Several studies have found schizoaffective manic patients with poor long-term prognoses, although it is unclear whether one can (13) or cannot (35) identify such a group with the schizophrenic subtype diagnosis or with the finding of recurrent or chronic schizoaffective mania in the absence of other affective episodes (26).

BIOLOGICAL MEASURES

Biological studies of schizoaffective patients have been reviewed by Meltzer and associates (38). Rare studies have included identified groups of patients with schizoaffective mania or schizoaffective mania, schizophrenic subtype, and relatively few have included any schizoaffective patients. No biological measures have consistently been reported to differentiate schizoaffective manic from schizophrenic or affective patients. Meltzer et al. (38) suggested that there may be biological similarities between affective subtype and affective disorder patients, on the one hand, and between schizophrenic subtype and schizophrenic patients, on the other, but there are few data to support this assertion. The lack of biological data may be due to 1) a low rate of schizoaffective mania in some settings, 2) difficulty in studying manic and schizoaffective manic patients in the unmedicated state because of their agitation, 3) failure to apply the RDC rigorously to differentiate schizophrenic subtype from schizophrenic patients, and 4) low priority on research in this area.

We suggest that there are many patients with schizoaffective mania—and particularly schizoaffective mania, schizophrenic subtype—in chronically impaired populations and that they deserve closer biological investigation. For example, it may be that there are neurophysiological substrates for both the similarities (chronic impairment with similar psychotic symptoms) and the differences (in affective responsivity, grandiosity, hyperactivity, etc.) between schizoaffective mania, mainly schizophrenic subtype, and schizophrenic disorders. There may be measurable biological correlates of these dimensions. Biological differences may prove to be related to etiology (whether genetic or acquired), to location of lesions having common etiologies, or to differential effects of lesions on different individuals.

RESPONSE TO TREATMENT

It is notoriously difficult to study drug response in manic illness. Patients are often uncooperative, the risks of agitation and violation make studies of acute response to lithium alone difficult, and poor compliance hinders the study of lithium prophylaxis in patients with chronic symptoms—about whose treatment the least is currently known. Therefore, it is not surprising that there are few controlled data about drug treatment of schizoaffective manic patients.

The available studies have been thoroughly reviewed by Goodnick and Meltzer (39); only the most relevant will be considered here. There have been only four double-blind studies of treatment with lithium alone for acute schizoaffective mania (40–44). Three of these studies used diagnostic criteria unrelated to current research criteria. The largest of these studies (40) differentiated 255 manic-depressive and 83 schizoaffective manic patients on the basis of *DSM-II* criteria. The schizoaffective manic patients had higher pretreatment ratings for a variety of psychotic symptoms and hostility. However, experience in the past 10 years suggests that patients with schizoaffective mania diagnosed according to *DSM-II* are likely to have a diagnosis of bipolar disorder or schizoaffective mania, affective subtype, by the RDC. The results for schizoaffective manic and manic patients were not directly compared in the published reports, which focused on the finding that "highly active" patients in both groups did better when taking chlorpromazine alone than when taking lithium alone. Examination of the separate tables of improvement scores for manic patients (41, p. 151) and schizoaffective manic patients (40, p. 186) suggests that manic patients showed more improvement with lithium, but no statistical analysis is available. In another pre-RDC study, Johnson (42) selected "schizo-affective excited" patients by criteria that appear more similar to those of schizoaffective mania, schizophrenic subtype; 15 of 19 manic patients definitely remitted on a regimen of lithium alone, compared with one of 11 schizoaffective patients (six of whom worsened). Brockington et al. (43), using the Kendell criteria shown in appendix 1, found lithium (N=6) as effective as chlorpromazine (N=5); however, as we have discussed, few of their "schizomanic" subjects met the RDC for schizoaffective mania, and most were manic according to the RDC. The only double-blind study to use the RDC (43) included only three patients with schizoaffective mania (subtypes not given); all improved.

In three double-blind studies, lithium was added to neuroleptic treatment. Two of these studies (45, 46) were small; they showed improvement in a total of six of eight patients with schizoaffective mania (subtype not given) when lithium was added to a stable dose of neuroleptics. The third study (47)—of acute treatment with lithium alone versus lithium plus haloperidol—included 13 schizoaffective mania, mainly schizophrenic subtype, patients (eight received lithium) and

23 affective subtype patients (10 received lithium) diagnosed by criteria similar but not identical to the RDC. The lithium group for each diagnosis did better on each of three rating scales, but differences were statistically significant only for the affective subtype group and only on one scale (the Brief Psychiatric Rating Scale).

Open acute drug studies are more difficult to evaluate. Zall and colleagues (48) were the first to suggest that lithium improved the manic, but not the schizophrenic, symptoms of schizoaffective manic patients. Pope et al. (7) found equal response to lithium in bipolar and schizoaffective manic patients (diagnosed according to the RDC; no subtype given), but treatment was by doctor's choice and data were retrospective. The most psychotic patients may have been those who received neuroleptics plus lithium. Goodnick and Meltzer (39) suggested that their schizoaffective manic patients responded to lithium, but over a longer period of time (up to 60 days). It has also been suggested (49), but not prospectively studied, that some patients may require higher lithium levels than are commonly used.

Only a handful of patients with schizoaffective mania have been treated with lithium prophylactically under double-blind, controlled conditions. Only six schizoaffective manic patients (out of 198) were included in the large NIMH study by Prien and associates (50). Mattes and Nayak (51) treated 12 schizoaffective mania, schizophrenic subtype, patients with fluphenazine (hydrochloride or decanoate) and lithium (more than 0.6 meq/liter) and then substituted placebo for one of the medications in a randomized, double-blind design. During 1 year of treatment, six of seven lithium-treated patients relapsed, but only one of five fluphenazine-treated patients did—a statistically significant difference despite the small numbers. Rosenthal et al. (52) stated that some of their 44 bipolar and 22 schizoaffective manic patients were treated in a double-blind design, but they did not separate these from openly treated patients in their report. They found that patients with schizoaffective mania fared slightly better than bipolar patients over a 5-year period, but their entry criteria systematically excluded those regarded as "atypical, eg, those with a history of long periods of psychosis in the absence of an affective syndrome, or those with clear evidence of deterioration between episodes" (8, p. 804). Thus, their schizoaffective manic group may have been biased toward more cooperative patients with good remissions, and all schizoaffective manic, schizophrenic subtype, patients would have been excluded. To our knowledge no other blind or open studies have been conducted using current research criteria for diagnosis. Early, open lithium prophylaxis studies of substantial numbers of schizoaffective patients (with all subtypes combined) were conducted by three groups: Hofmann et al., cited in Goodnick and Meltzer (39), studied 19 schizoaffective patients, Angst et al. (53) studied 72, and Smulevitch et al. (54) studied 49, all using World Health Organization or *DSM-II* diagnoses. The first two studies found less prophylactic effect in schizoaffective than in manic patients; the third found equally good results in the two groups.

Existing drug treatment studies, then, are limited by sample, methodology, and/or use of outmoded diagnostic criteria. A substantial number of patients with schizoaffective mania appear to derive acute and long-term therapeutic benefit from lithium treatment, but the patients studied have probably had primarily schizoaffective mania, affective subtype, or bipolar disorder. It remains unclear 1) whether either the frequency or the degree of drug response is equal to that found in manic patients and 2) how to identify those most likely to benefit. There are suggestions that the most schizophrenia-like symptoms show the least response to lithium, but this question has not been systematically studied, nor has the response to neuroleptics. Schizoaffective mania, schizophrenic subtype, patients may show the worst lithium response, but few patients have been studied (and none identified as such in studies of acute illness).

There have also been reports of effective treatment with ECT for patients with schizoaffective disorders, *DSM-II* schizoaffective schizophrenia, and "affect-laden" schizophrenia (55–59). It is unlikely that schizoaffective manic patients were well represented in these studies. Reported predictors of ECT success include acute illness, depressive affect, low self-esteem, hopelessness, and suicidal thoughts (60–63). In the one study that reported successful use of ECT in schizoaffective mania (59), only nine schizoaffective (schizoaffective mania and schizoaffective depression) patients were included, results for the schizoaffective manic subgroup were not discussed separately, the subjects were described as having a mainly affective type of illness, and data were examined retrospectively. The role of ECT in the treatment of schizoaffective mania therefore remains unclear. This issue particularly deserves investigation in schizoaffective manic patients with a chronic and drug-resistant illness and a poor outcome, for whom ECT may represent the treatment of last resort.

OVERLAP WITH OTHER CLASSIFICATIONS

A degree of overlap has been recognized between schizoaffective mania diagnosed by the RDC or similar criteria and several other proposed types of psychosis. These can be divided for convenience into two general groups: the atypical forms of schizophrenic or schizophreniform disorders and the cycloid psychoses.

It has been suggested that patients with schizophrenic combined with affective symptoms have a better outcome (good prognosis schizophrenia), although Gift et al. (64) reviewed the available studies and were unable to validate the claim. It is possible that some of the previously studied patients had atypical forms of depressive illness, as a family history of depression was considered an important diagnostic

criterion (65). More recently, Sautter and Garver (66) suggested that there is a type of acute schizophreniform psychosis that does not meet current criteria for affective disorder yet is characterized by therapeutic response to lithium alone and, frequently, by a positive family history of affective disorder. It is not known whether these patients have a distinct disorder, an atypical form of affective disorder, or simply a spontaneously remitting disorder.

A number of Scandinavian investigators have attempted to define a category of reactive psychosis (67). McCabe (68) suggested that such patients have brief episodes with psychologically meaningful precipitants, preserved affect, affective features without endogenous depression, and absence of schizoid features or a schizophrenic family history. In this and other studies of this syndrome, it is difficult to determine the precise psychopathology of the subjects, but there is apparently some association with favorable outcome. Stephens et al. (67) assigned RDC and *DSM-III* diagnoses to a group of patients previously diagnosed by Astrup as having either reactive (N=91) or schizophrenic (N=78) psychoses. The reactive patients had been shown to have a more favorable outcome (69). Over two-thirds of the RDC schizoaffective and unspecified functional psychosis patients were considered reactive, compared with only one-third of the RDC schizophrenic patients. It is unclear how many of these patients had features of schizoaffective mania.

Finally, Perris and colleagues (70, 71) attempted to define and investigate the concept of cycloid psychosis originated by Kleist and by Leonhard (72). Such patients have mixtures of schizophrenic and affective symptoms, usually with rapid variability within the episode of illness rather than separate affective episodes of single type, and a distinctive type of confusion or perplexity during the episode. They have good remissions but recurrent illness, with some apparent prophylactic effect from lithium (70) and, frequently, a similar type of illness in family members (71). The description bears a resemblance to Kasanin's (73) original definition of schizoaffective disorder: a "psychosis . . . characterized by a very sudden onset in a setting of marked emotional turmoil with a distortion of the outside world and presence of false sensory impressions in some cases. The psychosis lasts a few weeks to a few months and is followed by a recovery" (p. 122). However, current concepts of schizoaffective disorder emphasize the co-occurrence of complete schizophrenic and affective syndromes rather than features of the onset and course. Many cycloid patients are indeed diagnosed as schizoaffective by the RDC, although most schizoaffective patients do not meet criteria for cycloid psychosis (71). The validity of this diagnosis and its possible relation to schizoaffective mania and other schizoaffective disorders are unknown.

We have noted that some patients who might be considered either reactive or cycloid have several of the following features of what would at one time have been considered hysterical psychosis: vivid current or past visual hallucinations, absence of thought disorder, preserved affect, variable presentations leading to multiple psychotic diagnoses, unpredictable improvement, apparent manipulative use of symptoms, lack of response to neuroleptics, and nonneurological gait disturbance. While some of these patients remit, others have a chronic course punctuated by exacerbations. Many are given schizoaffective diagnoses because of mixed and variable symptoms but may not convincingly fit either the schizophrenic or affective syndrome.

CONCLUSIONS

It would be premature to conclude that schizoaffective mania can now be understood as simply a variant of bipolar disorder. At least two subtypes can be identified, as defined by the RDC: one with mainly affective and one with mainly schizophrenic features, particularly the presence of chronic thought disorder or delusions in the absence of mania or depression. It is likely that further clinically meaningful distinctions can be made: 1) consecutive versus concurrent appearance of the schizophrenic and affective components, 2) recurrent or chronic schizoaffective manic episodes versus a bipolar course, and 3) presence versus absence of substance abuse or other known organic factors. Family history and biological (including genetic, structural, physiological, and biochemical) measures may also provide a basis for subtyping in the future.

There is a growing consensus on the basis of evidence from family history, clinical features, and lithium responsiveness that schizoaffective mania, affective subtype, patients have a form of bipolar disorder with non-mood-congruent features as defined in *DSM-III*. Misdiagnosis of these patients as schizophrenic is a persistent problem. However, it is not known why such patients have more schizophrenia-like psychotic symptoms than other bipolar patients; it has been proposed that there may be a distinct, perhaps familial, vulnerability to psychotic features (25). There are many bipolar patients with chronic illness and substantial long-term disability, although this group may not entirely overlap with those with schizoaffective mania, affective subtype. Further investigation of such bipolar subgroups is needed.

There is too little evidence to determine the relationship of schizoaffective mania, mainly schizophrenic subtype, to affective or schizophrenic disorders. Neither family nor treatment studies have investigated this group in sufficient numbers, but there are data to suggest that these patients may have more familial schizophrenia and less familial affective disorder than patients with the mainly affective subtype and that they respond more poorly to lithium. It appears likely that the mainly schizophrenic subtype is a heterogeneous group including a subgroup of schizophrenic patients whose symptoms mimic mania, a subgroup of schizophrenic patients with chance occurrence of an affective disorder or component, an atypical group of

bipolar patients, and patients with a distinct disorder. This disorder is apparently rare in some treatment settings and not uncommon in others. In our experience, it is most common in state hospitals and among community patients who receive minimal or "revolving door" treatment, possibly because these patients' chronicity and high level of psychopathology lead to abandonment by social support systems.

Clinically, the trend toward assessing responsiveness to lithium (and other antimanic treatments) in all such patients is an important one and should not be reversed; too little is known about schizoaffective mania, schizophrenic subtype, to predict which patients might derive benefit. However, many clinicians (ourselves included) have seen multiple schizophrenic subtype patients fail to derive much benefit from lithium or carbamazepine. Particularly for those who treat chronic patients, it is common to feel torn between pessimism, on the one hand, and guilt (because of the many articles stressing the affective nature of schizoaffective mania), on the other. Our own strategy is as follows: whenever possible, a lithium trial is undertaken for both affective and schizophrenic subtype patients. The diagnostic reason for the trial is clearly discussed in advance, with full awareness that the success rate for the schizophrenic subtype patients may prove to be low. A full trial of acute treatment (1–2 months with lithium levels preferably over 1.0 meq/liter) is then given under conditions that permit reaching a meaningful conclusion. These conditions include either a trial of lithium alone, lithium added to a previously stable neuroleptic regimen, or lithium plus neuroleptics, with tapering of the neuroleptic after improvement has occurred in order to assess the contribution of lithium. If benefit cannot be documented, lithium is discontinued, with careful observation for any subsequent deterioration that might imply an unnoticed benefit from the lithium. In some cases more than one such sequence is necessary (usually on separate admissions) to determine whether adding lithium is more beneficial than treatment with neuroleptics alone. Too little is known to guide the choice of patients for trials of carbamazepine with or without lithium, although from anecdotal evidence it appears that affective rather than schizophrenic subtype patients would be most likely to benefit.

The potential heterogeneity of schizoaffective mania is further underscored by the fact that several other proposed types of distinct psychoses show considerable overlap with schizoaffective categories. It remains unclear which is the better diagnostic framework for some of these patients.

We conclude, therefore, that schizoaffective mania, as currently defined, is a heterogeneous disorder. Some but not all schizoaffective manic illness appears to represent a variant of bipolar disorder. The genetics, treatment response, and longitudinal course of these disorders remain inadequately studied, and drawing premature conclusions should be avoided in the absence of such evidence.

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APPENDIX 1. Diagnostic Criteria for Schizoaffective Mania

TSUANG AND DEMPSEY (9)

1. Chart diagnosis of schizophrenia on index admission
2. Not schizophrenia or depression (Feighner criteria) because of either:
   a. Brief duration *or*
   b. Having features of a second disorder
3. Either:
   a. Affective symptoms present at index admission *or*
   b. Previous remitting episode

WELNER ET AL. (10)

1. One of the following:
   a. Depression according to Feighner criteria (similar to RDC) *or*
   b. Mania according to Feighner criteria *or*
   c. Mixed mania and depression (six symptoms from these syndromes)
2. Two of the following thought and behavior disorders:
   a. Delusions
   b. Hallucinations
   c. Formal thought disorder (not circumstantiality or flight of ideas)
   d. Inability to communicate logically
   e. Bizarre or strikingly inappropriate behavior
3. Acute onset *or* episodic course *or* perplexity/confusion/bewilderment
4. Not alcohol, drug abuse, or other organic disorder

KENDELL (11)

1. Meets three criteria for mania (with two "partial" symptoms counting as one "full"): euphoria, racing thoughts, tirelessness, delusions of special powers, delusions of grandiose identity, overactivity, distractibility, irreverent behavior, embarrassing behavior, hypomanic affect, pressure of speech, flight of ideas
2. Meets criteria for one of the following:
   a. Schizophrenia: one nuclear symptom (thought insertion, withdrawal, or broadcasting; echo of thoughts; voices discussing the patient; delusions of control; autochthonous delusions) or specific behavior, affect, and speech symptoms if patient is not interviewable
   b. Paranoia: preoccupying delusion involving the external world (delusions of influence, persecution, reference, misinterpretation, assistance, infidelity, fantasy lover)

ABRAMS AND TAYLOR (12)

1. Meets criteria for mania (all of the following: flight of ideas or grandiosity; rapid or pressured speech; euphoric, expansive, or irritable mood)
2. One or more first-rank symptoms (audible thoughts, voices conversing about the patient or commenting on his or her thoughts or behavior, experiences of influence or alienation, delusional perception)

HIMMELHOCH ET AL. (13)

1. Meets RDC
2. Formal thought disorder or delusions present between episodes

RESEARCH DIAGNOSTIC CRITERIA (6)

1. Distinct period with elevated, expansive, or irritable mood (may alternate with depression)
2. Three of the following (four if mood is only irritable):
   a. Hyperactive physically or in social, work, home, or sex life
   b. More talkative than usual or pressure of speech
   c. Flight of ideas or feels thoughts are racing
   d. Inflated self-esteem
   e. Decreased need for sleep
   f. Distractibility
   g. Poor judgment (engaging in activities without awareness of potential harm: fast driving, sex, etc.)
3. At least one core schizophrenia-like symptom:
   a. Delusions of being controlled or thought broadcasting, insertion, or withdrawal
   b. Hallucinations not congruent with manic or depressed mood
   c. Auditory hallucinations of running commentary on thoughts or two or more voices conversing
   d. Delusions of hallucinations during 1 week without prominent affective symptoms
   e. One week without prominent manic symptoms but with marked formal thought disorder *and* either 1) blunted or inappropriate affect, 2) delusions or hallucinations, or 3) grossly disorganized behavior
4. Duration of at least 1 week; residual symptoms after recovery may be affective and/or schizophrenic
5. Affective symptoms overlap with an active period of schizophrenia-like symptoms
6. Subtypes:
   a. Mainly schizophrenic; one of the following:
      1) Schizophrenic symptoms present 1 week in the absence of manic or depressive features *or*
      2) Prior to affective features, had social withdrawal, impaired occupational functioning, eccentric behavior, emotional blunting, or unusual thoughts or perceptual experiences
   b. Mainly affective: both of the following:
      1) Schizophrenia-like symptoms followed manic or depressive symptoms and were never present for 1 week without them *and*
      2) Good premorbid social and occupational adjustment
   c. Other: meets criteria for neither mainly schizophrenic nor mainly affective subtype
7. Course: criteria are provided for acute, subacute, subchronic, and chronic course of illness

MAJ AND PERRIS (14)

1. Type I: consecutive appearance of two syndromes:
   a. Affective subtype: schizophrenia-like onset with recurrent affective course
   b. Schizophrenic subtype: affective onset with later progressive schizophrenic course
2. Type II: concurrent syndromes:
   a. Axis 1 (cross-sectional syndrome): manic versus depressive (criteria similar to RDC, from Comprehensive Psychiatric Rating Scale items)
   b. Axis 2 (course):
      1) Affective subtype: previous schizoaffective and/or affective episodes, each followed by full remission
      2) Schizophrenic subtype: residual schizophrenic symptoms (as defined) upon which schizoaffective episodes are superimposed
      3) Other (pattern different from affective and schizophrenic subtypes); unspecified (new disorder or no information available)
   c. Axis 3: whether associated with organic mental disorder, alcohol or drug abuse, long-term use of antipsychotics, or long-term use of antidepressants

Patient Attrition in Dynamically Oriented Treatment Groups

Howard B. Roback, Ph.D., and Maribeth Smith, M.A.

Clinical and empirical studies of premature terminators from dynamically oriented therapy groups are reviewed. While many studies focus on the personality characteristics of dropouts, the authors recommend conceptualizing such patients in terms of the interaction of patient, group, and therapist. On the basis of this model, the authors offer clinical recommendations for reducing the number of dropouts. Multivariate experimental designs for studying attrition in group psychotherapy are discussed, and the authors suggest possible directions for future research.

(Am J Psychiatry 1987; 144:426–431)

While there is a core research literature on the dropout from individual psychotherapy (1–6), the body of knowledge on the patient who prematurely terminates group psychotherapy is sparse (5, 7). Although this discrepancy is primarily attributed to the difficult methodological problems in studying something as complex as multiperson interaction, attrition in group therapy may have more serious clinical consequences than in its individual counterpart. For example, in addition to failing to benefit from the therapeutic opportunity accorded the dropout from individual psychotherapy, the group therapy discontinuer may adversely affect the therapeutic potential of the group for other patients. That is, his or her discontinuation may disrupt group solidarity, create a "wave effect" (i.e., precipitate other dropouts), or have a disquieting effect on the therapist (7–9).

In this paper, clinical and research findings on adult patient attrition in dynamically oriented therapy groups are reviewed. The findings addressed are 1) its incidence, 2) major patient, setting, and therapist factors that appear to contribute to defection from treatment, 3) the importance of conceptualizing these factors in a multicomponent model and viewing premature termination as the result of their conjoint influence, 4) means available to group therapists for reducing treatment dropouts, and 5) recommendations for research on the dropout phenomenon.

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INCIDENCE

Table 1 presents attrition figures and characterizations from 11 dynamically oriented adult psychotherapy groups (8–18) reported on in the literature. These studies were selected because the authors were careful to provide readers with information on the therapists, treatment approach and setting, patient characteristics, and dropouts. The summarized information illustrates a number of issues that complicate cross-study comparisons. Even within the select category of dynamically oriented group psychotherapy, significant variations exist in group emphasis, therapists, patient population, and dropout criteria.

Dynamically oriented group psychotherapy has been described as "the opportunity to examine interpersonal functioning and to reflect upon intrapsychic processes that contribute to overt behavior" (10). However, it has been demonstrated that generic labels identifying group orientation may have remarkably little bearing on actual process events. For example, in the widely cited comparative group outcome study by Lieberman et al. (19), one Gestalt group had the most casualties, while another Gestalt group was the most beneficial. The descriptions of therapeutic emphasis in the studies cited in table 1 range from short-term psychodynamically oriented to psychoanalytic. Although the authors presented descriptions of therapy style, few directly verified the approaches used. Furthermore, the groups varied from short- to long-term, and they included both experienced and inexperienced therapists (both categories are somewhat arbitrarily defined). In two studies (16, 18) the dropout rates were based on combined inpatient and outpatient data.

Baekeland and Lundwall (5) have raised other methodological concerns that make incidence comparisons across studies difficult. Dropouts are often imprecisely defined and include both persons who fail to show up for the first session and those who remain in therapy for almost a year before terminating. Intuitively, it would be assumed that there are identifiable differences between nonstarters and later dropouts. In addition, dropouts are inconsistently defined; in some studies the criterion is failure to complete the fixed time period for the group's existence, and in others it is

TABLE 1. Studies on Attrition From Dynamically Oriented Outpatient Psychotherapy Groups[a]

Study	Type of Group	Therapist Level	Number of Participants	Dropouts	
				Time	Cumulative Percent
Yalom (8)	Dynamic, intensive, interactional	Trainee	97	12th session	36
Yalom et al. (9)	Dynamic, intensive, interactional	Trainee	40	12th session	27.5
				20th session	42.5
Stone and Rutan (10)	Long-term, psychodynamic	Experienced	147	6 months	19.5, therapist A; 30.8, therapist B
				1 year	39.0, therapist A; 38.4, therapist B
Lothstein (11)	Expressive-dynamic	Primarily trainee	47	12th session	29
Nash et al. (12)	Dynamic	Trainee	30	4th session	57
Koran and Costell (13)	Psychodynamic-interpersonal	Trainee	87	12th session	13
				20th session	17
Stone et al. (14)	Psychodynamic-group dynamic	Trainee	42	6 months	14
				1 year	50
Budman et al. (15)	Short-term (15-session limit), psychodynamically oriented	Experienced	192	5th session	16.6
Weiner (16)[b]	Psychoanalytically oriented	Experienced	100	10th session	24
Piper et al. (17)	Short-term (6 months) and	Experienced	23	6 months	17
	long-term (24 months), psychodynamically oriented		26	24 months	27
Grotjahn (18)[b]	Psychoanalytic	Experienced	122	12 months	35
				18 months	63

[a]The group members primarily had personality disorders or neurotic conditions. Psychotic patients, substance abusers, sexual offenders, and sociopaths were typically excluded from these groups.
[b]A small number of inpatients were included.

termination after a given number of sessions or length of time. Few studies apart from that of Stone and Rutan (10) break down the dropouts according to whether they belonged to the original group membership or had joined the group at a later point. One might also inquire how investigators classified patients who dropped out but later rejoined their groups.

The discontinuities among studies enable one at best to make only gross estimates of premature termination rates. Although table 1 reveals appreciable differences in attrition figures (range=13%–63%), the numbers cited are alarming when one considers that clinicians are committed to the belief that improvement is predicated on a patient's continuance in treatment. Further, since an important goal of dynamically oriented group therapy is to enhance a person's adaptive interpersonal behavior, dropping out of therapy would be prima facie evidence that this goal was not achieved (3).

We believe that dropping out of treatment is usually a complex interaction between patient, group, and therapist factors, but much of the literature tends to focus on only one of these dimensions. We will first review these single-factor contributions, then discuss how one might conceptualize the dropout phenomenon in terms of conjoint or interactional influences.

PREMATURE TERMINATION

Patient Factors

Several patient characteristics are commonly observed to identify persons at risk for prematurely leaving dynamically oriented group psychotherapy. The majority of patient factors are characterological defenses that result in major interpersonal deficits. Included in this category are problems with self-disclosure, difficulties with intimacy, generalized interpersonal mistrust, excessive use of denial, and a tendency to be either verbally subdued or hostile (8, 10, 12, 15, 16, 20). As noted by Dies and Teleska, "Maladaptive interpersonal styles which have led [a patient] to seek therapy in the first place, may unfortunately prove to be self-defeating in that context as well" (21, p. 123).

Other patient factors reportedly associated with therapy discontinuance include situational states of the patient. Weak motivation for and unrealistic expectations of therapy and therapeutic change are often prognostic of patient flight (13, 16, 18). Similarly, a person brought into a group during a period of acute crisis tends to leave treatment as soon as the crisis is resolved. While many therapists view the latter behavior as dropping out, patients appear to view such crisis resolution as completion of their therapy. Another situational factor that appears to be associated with premature termination is socioeconomic status. Although the empirical data are not definitive, higher dropout rates appear to be associated with lower socioeconomic status (1, 12, 13, 22, 23).

Weiner addressed the "seasonal premature terminator," the patient who defects from therapy shortly before, during, or after a therapist's vacation. Such a patient is believed to "feel deserted by a parent and left with nonsupportive siblings" (24, p. 218); he or she then identifies with "the aggressor—becoming

one who leaves instead of one who is left" (24, p. 218).

Group Factors

Although less important than the aforementioned patient factors, characteristics of the group itself have been described as influential in patient attrition. This category includes both the group's structural and dynamic properties.

Structural components are the group's organizational characteristics. One such variable is duration of therapy (e.g., long- versus short-term). In the studies reviewed in this paper, lower percentages of dropouts appeared to occur in short-term groups (15, 17). It may be that a short-term group has a clearer structure and a more organized agenda—characteristics cited as being associated with lower attrition (25). These factors may maintain motivation and reduce resistance by providing patients with tangible goals and accomplishments. Short-term therapy may also enable the patient to keep the end in sight, making him or her more willing to complete the set course of treatment.

Dynamic properties of therapy groups have also been cited as promoting attrition. A low degree of cohesion is the most common dynamic component considered to lead to early patient withdrawal from groups. Patients in such groups often feel a lack of support, belonging, and mutual understanding (12), thus heightening their distress and lessening their perception of the group as potentially helpful. Scapegoating is another group dynamic that often results in patient dropouts. In other words, a group identifies a deviant member and, possibly in an attempt to create unity, pressures that person to conform to group norms or withdraw from the group (11). Also cited is the "wave phenomenon," i.e., "contagious" withdrawal within a group. This usually results from the withdrawal of a member who has been instrumental in maintaining particular relationships or roles, causing upset in the dynamic group system. While dynamic components are perhaps the most difficult to operationalize and investigate, their potentially significant influence demands closer examination.

Therapist Factors

A few studies have cited therapist factors as causes of premature withdrawal from group psychotherapy. Nash et al. (12) found that several patients who dropped out of group therapy felt "remoteness" and "lack of support" from their therapists. Although such an experience may be due to a therapist's personality or therapeutic style, it may also be the result of countertransference issues (1, 11, 18). For example, Lothstein found that therapists in his study "disliked the patients who dropped out" (11, p. 1494).

Intuitively, it would seem that a therapist may contribute to attrition by being insufficiently aware of factors associated with premature termination. While quality of group training and experience level are likely to be related to such an awareness, a therapist's ability to detect and predict patient and group malfunction may also depend on his or her degree of psychological mindedness and theoretical orientation.

While the isolation of factors associated with premature termination may be useful in the initial stages of inquiry, a richer understanding comes from simultaneously considering several dimensions of psychotherapy groups. We share the view of others (7, 8, 18, 26) that the most productive analysis of the dropout phenomenon will come from studying the interactional effects of the patient, group, and therapist. As noted by Koran and Costell, "The decision to terminate therapy, like the decision to begin it, depends on multiple influences. . . . The more of these factors one can take into account, presumably the better one should be able to identify patients highly likely to terminate early" (13, p. 348). We now turn to a discussion of how premature termination may be better understood in terms of the simultaneous influences of patient, group, and therapist variables. Although all three of these dimensions certainly operate simultaneously, for clarity we will discuss only two group process dimensions at a time.

INTERACTIONAL MODEL

Patient×Group

A conceptualization focusing on the patient-group interaction considers the attributes of the patient in conjunction with the composition and dynamics of the individual's particular group. Interplay between the two dimensions is supported by such observations as those of Bach, who stated, "Certain patients who have the most intensive conflicts in one group find it relatively easy to communicate and participate in another group without any remarkable therapeutic effects having taken place in the switch" (26, p. 301). The compatibility of patient and group seems an important area for investigation, not only to reduce attrition rates but also to maximize the therapeutic potential for all patients.

Patient×Therapist

Just as a patient may not "fit" in a specific group, there may also be disturbance between a patient and therapist. Several authors (1, 11, 18, 24) mention patient-therapist transference/countertransference issues and dissimilar expectations about the patient-therapist relationship as major factors in a patient's flight from therapy. Since the therapist is unlikely to withdraw from the group, the patient bears the consequences of such a mismatch. In some instances, the patient, sensing the therapist's desire to be rid of him or her, may simply cooperate with the therapist's unconscious by dropping out of the group (27).

Therapist×Group

It is highly unlikely that any one therapist is equally effective at working with all types of groups and all patient populations. A therapist-group miscombination may interfere with maintaining an intact therapeutic unit. This is less likely to occur with more experienced therapists than with therapists-in-training, who have yet to discover their optimal therapeutic situations.

The effect of the complex interplay between patient, group, and therapist factors on premature termination can be illustrated by the dropout rates in the studies in table 1. For example, in the Nash et al. (12) study, trainees conducting dynamically oriented groups with patients from low socioeconomic classes had an unusually high rate of dropouts. If this were a replicated finding, we would conclude that the combination of therapist inexperience, dynamic orientation, and patients from low socioeconomic classes results in a poor prognosis for the patients' continuance in group psychotherapy. However, this would not tell us which interacting factors contribute most to premature termination. That is, there are four possible combinations of these three factors: A×B, B×C, A×C, and A×B×C. This example illustrates the need for multivariate research, which will be discussed later in this paper. A fourth dimension, external factors (e.g., transportation problems, scheduling conflicts) may also contribute to premature termination, but clinical experience suggests that such reasons often mask deeper motivations.

Thus far the paper has illustrated how the group therapy dropout phenomenon can be conceptualized through an interactive rather than a single-factor model. The interaction model seems preferable because consideration of a main effect in isolation from other factors has produced highly discrepant explanations of premature termination. These discrepancies are understandable if early withdrawal is the result of conjoint or interactive effects rather than of any one factor alone. Further, if premature termination depends on a single factor, then certain patients, therapists, and/or groups would consistently prove futile in sustaining therapy. The clinical and experimental literature do not support such a position.

The interactive model should prove useful to the group therapist by helping to provide a clearer conceptualization of how standard clinical practices can be used to prevent premature termination.

PREVENTIVE MEASURES

Initial Screening

The common practice of patient screening and selection parallels the previously discussed need for suitable patient-group match. Much of the literature on patient selection has focused on its role in building cohesion (20, 28). From our perspective, careful patient screening may also serve to prevent dropouts resulting from patient-group mismatches. For instance, findings from studies and clinical reports cited earlier in this paper indicate that persons likely to disturb the communication flow within a group or who become isolated from the communication network ultimately become "group deviants" and are the most vulnerable to dropping out.

Stone et al. (14) found a prior history of individual therapy or concurrent individual and group therapy to characterize the patients who remained in dynamic group treatment. Similarly, Yalom (8) found that his "group deviants" had significantly less prior individual therapy than other group members. However, as Yalom asked, Has prior individual therapy increased the psychological mindedness of the patients who remain in group therapy, or because of their deemphasis on psychological factors, have future deviant patients typically avoided intensive individual therapy? It appears that personality traits such as denial, deemphasis on intrapsychic and interpersonal factors, and increased emphasis on somatization and environmental factors should be particularly explored during the screening of a patient with no prior history of individual care.

Goldstein et al. (29) have advocated trial groups as a means of improving on the traditional interview basis for group composition. In their behavioral-observational format, potential group members would be rotated through reconstituted groups and their interaction rate, leadership behavior, etc., would be observed. By this means, Goldstein et al. believe one could place patients into the most appropriate therapy groups. Similarly, Budman et al. (30) reported good results from using a pregroup preparatory workshop as a screening tool for patients being evaluated for short-term group psychotherapy.

Instead of asking the traditional question, "Is this patient a good candidate for group psychotherapy?" the interactive perspective asks more specifically, "Is this patient suitable for this particular group?" While further investigation is needed, we feel that this latter approach to screening patients for group psychotherapy may be a key to reducing dropout rates.

Group Preparation

The clinical practice of group preparation is employed to ensure that each patient has realistic expectations concerning the process of therapy (attitudes, motivations, and behavior) and improvement (1). Yalom (20) pointed out that some therapists provide prospective members with written material, let them listen to a tape of a session, or have them attend a trial session as a means of introducing them to group psychotherapy. Strupp and Bloxom (31) used a role induction film to prepare patients for group psychotherapy. The interactional model clarifies the purpose of preparatory techniques—namely, to prevent patient-group or patient-therapist conflicts that might

result from dissimilar expectations. If mutual expectations cannot be achieved, the patient should be informed that he or she is not suitable for a particular group and be provided with an appropriate referral.

Therapist Support

In addition to patient-group conflicts that may lead to premature termination, the therapist must also be sensitive to the patient-therapist issues that contribute to dropout rates. Because members need to perceive the therapist as caring and concerned about individual group participants (12), disturbances in the patient-therapist alliance due to real relationship or transference/countertransference issues must be confronted to prevent defection. Discussion of feelings toward individual members with one's cotherapist or a trusted colleague can prove helpful in resolving such conflicts.

The preventive measures just discussed are by no means new to clinical practice with groups. However, the interactional framework of group processes provides them with a rationale, or theoretical framework, that clarifies their function. Even so, because the factors leading to group discontinuation are multidetermined, dropouts will not always be avoidable.

To study complex issues such as premature termination from group psychotherapy, methodological refinements in future experimental protocols are needed. Such studies will be vital to the advancement of clinical practice and should be systematically addressed. Although detailed methodological, measurement, and statistical recommendations go beyond the scope of this paper, the importance of multivariate designs is addressed in the next section.

RESEARCH RECOMMENDATIONS

Research efforts are needed not only to provide reliable and validated predictive models for therapy dropouts but also to help conceptualize a theoretical basis for the process of premature termination. The importance of a predictive model of patients vulnerable to early withdrawal is readily apparent. If a therapist is alert to indications of defection, tactics may be implemented to retard its occurrence. The inconsistent and varied reports in the literature of factors believed responsible for patient withdrawal seem to support a multivariate model of the dropout phenomenon.

While multivariate designs (32) are highly complex, they may be the means to information about premature termination that has thus far gone undetected. For example, discriminant analysis will provide data regarding the relative power of the specific patient, group, and therapist variables that discriminate treatment dropouts from patients who remain. Simply stated, in discriminant analysis relevant variables become weighted according to their ability to predict differences between dichotomous groups (e.g., dropouts and remainers). Another multivariate analysis, multiple regression, might prove helpful in predicting the length of time patients remain in therapy. In both cases, the investigator is able to account for multiple influences, providing a more detailed account of cases of defection.

From a practical point of view, it is important to follow trends in a group. That is, it is necessary to collect data from various sources and at various times in the group's history. For example, a patient's role in the group may change over time and may be perceived differently by the patient, group, and therapist. One could also evaluate interaction patterns and identify patients remaining on, or moving toward, the periphery of the group (e.g., becoming sociometrically ignored or rejected). Rose (33) reported on a brief questionnaire that is completed after each group session, measuring cohesion, self-disclosure, involvement, and satisfaction. From a research perspective, such instruments should enable the investigator to assess changes in the patient's participation level, sense of belonging, and satisfaction that are associated with changes in the dynamics of the group (e.g., shifts in intensity and goals). Clinically, such ongoing evaluations should prove helpful in early detection of group problems. Interested readers should familiarize themselves with other conceptual and methodological recommendations for studying small treatment groups (19, 33–36).

Several directions for future research can be drawn from the findings presented in table 1. For example, since group investigators (10, 16–18) have demonstrated that defection does not necessarily occur in an early phase, future studies should attempt to discriminate between those factors that predict early and late premature termination. Short- and long-term follow-up of patients terminating at various phases of treatment are virtually nonexistent (14). Data on whether the incidence of dropouts varies according to specific group formats (i.e., cognitive, behavioral, psychodynamic) and length of treatment (brief versus long-term) are also sparse. The relationship between family environmental variables (pathologies, attitudes, and behavior) and dropping out has received minimal investigation (37). Studies such as these should have both theoretical and clinical significance.

In sum, the development of predictive models should enrich our understanding of the process of premature termination. However, the development of such models requires sophisticated experimental designs and analyses to account for the simultaneous influence of several factors on patient attrition. Understanding this process will enable therapists to employ the most effective means for reducing the dropout rate in group psychotherapy.

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A Retrospective Study of Adolescents' Visits to a General Hospital Psychiatric Emergency Service

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Characteristics of 100 visits by adolescents (less than 18 years old) to a psychiatric emergency service were examined and compared with those of 100 visits by adults. Adolescents were less likely than adults to receive diagnoses of psychosis and personality disorder but more likely to receive diagnoses of adjustment and conduct disorders, were less likely to have had previous psychiatric treatment but equally likely (40%) to be in current treatment, and required more time to evaluate. Self-destructive ideation or behavior was present in 40% of the adolescents. Nearly all visits were judged to have represented genuine emergencies.

(Am J Psychiatry 1987; 144:432–436)

Adolescent mental health is an area of pressing national concern, especially given the dramatic and well-documented rise in adolescent suicides over the last two decades (1–3). General hospital emergency services or, if available, psychiatric emergency services are often the adolescent's entry point into the mental health system, and they frequently determine whether the adolescent will be treated in the inpatient or the outpatient segment of the system (4). Adolescents are usually seen by these emergency services at times of crisis when therapeutic interventions would be expected to have a major impact on their lives (5). Unfortunately, however, even when available, general hospital psychiatric emergency services tend to be geared toward adult patients. While a large number of adolescents are seen by such services, adolescents generally make up only a small percentage of all patients seen in any particular service (6, 7). Adult-oriented staff members often lack a conceptual framework for assessment of psychiatric emergencies involving adolescents and may, therefore, feel burdened and helpless in their work with these patients and their families. Furthermore, to our knowledge, research into characteristics of psychiatric emergency patients has not focused on the particular characteristics of adolescents coming for emergency treatment.

The present study examined the clinical characteristics of adolescents seen in a psychiatric emergency service and compared them with adult patients seen in the same setting. This study examined similarities and differences between adolescent and adult psychiatric emergencies in order to allow better understanding of the emergency needs of adolescents and better planning of services to meet those needs.

METHOD

The university hospital psychiatric emergency service is the only 24-hour, 7-day-a-week psychiatric emergency facility in an urban county of 900,000. It is by far the largest center in the area for psychiatric evaluations, although there are other centers where emergency medicine physicians will see psychiatric as well as all other problems. The psychiatric emergency service serves a total catchment area of 1,500,000 and sees about 20 patients a day. Its population is similar to psychiatric emergency room populations described in Cleveland (6), New Haven (7), and Durham (8) and consists primarily of young adults and lower socioeconomic status patients. Anyone 13 years of age or older may register as a patient. The service is the main point of entry into the state hospital system and the univer-

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The authors thank James Henry for his assistance with statistics and data analysis.

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sity hospital, and it is a significant point of entry into other private hospitals and the community mental health system.

In order to have access to more data than are routinely abstracted for statistical purposes, we retrospectively reviewed records from 100 visits by adults and 100 visits by adolescents chosen by random sampling from all adult and all adolescent patients seen during the calendar years 1983 and 1984. The 100 adult visits were made by 99 different individuals, and the 100 adolescent visits by 92 different individuals. Since patients 18 years of age and older are treated in the adult mental health system in Ohio, for the purpose of this study adolescents were defined as individuals 17 and younger. Each chart reviewed generally contained notes by a master's level psychiatric social worker and a psychiatrist and sometimes by other mental health professionals. Diagnoses were based on *DSM-III* criteria. We rated 41 clinical variables for each case, with a high degree of interrater reliability. If there was no notation in the record that a given clinical problem existed (e.g., hallucinations), the problem was recorded as absent. We also rated the acuteness of each visit on the basis of Rosenn's classification of adolescent psychiatric emergencies (9) and rated suicidal tendencies, suicide intent, and medical lethality of attempts by using the scales contained in the pediatric version of the Schedule for Affective Disorders and Schizophrenia (10). Chi-square statistics with a single degree of freedom were calculated with Yates' correction.

RESULTS

During 1983–1984, there were 14,203 patient visits to the psychiatric emergency service. Of these, 3.9% were made by 13–17-year-olds, 42.4% by 18–29-year-olds, 25.3% by 30–39-year-olds, 12.9% by 40–49-year-olds, 8.6% by 50–64-year-olds, and 6.9% by individuals 65 and older. Although the percentage of 13–17-year-olds was low, the actual number of visits was 591.

The samples of adolescents (N=92) and adults (N=99) did not differ significantly from the overall psychiatric emergency service populations of adolescents and adults in terms of age, sex, or race. The age distribution of the sample of adolescent visits was as follows: 13-year-olds, N=4; 14-year-olds, N=18; 15-year-olds, N=13; 16-year-olds, N=28; 17-year-olds, N=37. Thus, there was a preponderance of middle adolescents. When middle adolescents (ages 15–17) were compared with younger adolescents (ages 13–14), there were no significant differences in any of the variables in the following discussion.

Table 1 compares the demographic characteristics of adolescent and adult visits to the psychiatric emergency service. Both groups were about evenly divided between males and females, and both reflected the city's racial composition (about two-thirds white and one-third black). Nearly all of the adolescents were single, as opposed to less than half of all adults. Adolescents were less concentrated in the inner-city area around the medical center than were adults and

TABLE 1. Characteristics of 100 Adolescent and 100 Adult Visits to a Psychiatric Emergency Room

Characteristic	Number of Visits: Adolescent[a]	Number of Visits: Adult[a]	χ^2	df	p
Demographic					
Sex			2.02	1	n.s.
Male	61	50			
Female	39	50			
Race			1.09	1	n.s.
White	70	62			
Black	30	38			
Marital status[b]			55.97	2	<.0001
Single	97	48			
Married	2	30			
Divorced, widowed, or separated	1	17			
Catchment area			9.27	1	<.005
Local	21	42			
Other	79	58			
Insurance[b]			22.41	2	<.001
None	31	52			
Medicare/Medicaid	32	41			
Private	32	7			
Presentation					
Referral source			24.06	3	<.001
Self	11	40			
Family/friends	20	8			
Medical emergency room	31	23			
Other	37	28			
Presenting complaint[b]			26.56	10	<.005
Substance abuse	9	10			
Suicidal ideation	11	6			
Suicidal gesture/attempt	25	11			
Other self-destructive behavior	4	1			
Depression/insomnia	6	7			
Anxiety	4	10			
Hallucinations/delusions	0	8			
Inappropriate behavior	12	16			
Wants medication or hospitalization	1	9			
Physical symptoms	9	7			
Other	7	7			
Precipitant[b]			19.46	4	<.001
Death of loved one	3	6			
Family problems	24	7			
Primary relationship problems	8	19			
Other interpersonal problems	10	6			
Other or multiple precipitants	37	58			
Living situation[b]			94.78	5	<.001
Both parents	24	8			
One parent	39	4			
Institution	18	7			
Other relative	6	3			
Spouse	2	22			
Alone	0	36			

[a]Adolescent=13–17 years old; adult=18 or older.
[b]Data not available for all visits.

were more likely than adults to be covered by private insurance.

Adolescents were more likely to have been referred by family, friends, or by other agencies, whereas adults were typically self-referred (see table 1). With regard to chief presenting complaint, adolescents more often reported suicide attempts, ideation, or gestures or other self-destructive behavior (e.g., reckless driving), while adults were more likely to have been seen because of psychotic behavior, expressed anxiety, or the wish for medication or hospitalization. Fully 40% of the adolescents seen had a presenting complaint of suicidal behavior or ideation or other self-destructive acts. The precipitant for the current visit was more likely to have been a single problem (most frequently problems with family members) for adolescents and multiple problems for adults. Adolescents were, of course, more likely to have been living with their parents at the time of the emergency room visit than were adults and were more likely to have been living in institutional settings; most adults were living with a spouse or alone.

Adolescents were less likely than adults to have previously visited the psychiatric emergency service (N=24, 24%, versus N=53, 53%; $\chi^2=17.76$, df=1, $p<.0001$) and were less likely to have had past outpatient treatment (N=33, 40%, versus N=61, 69%; $\chi^2=14.52$, df=1, $p<.0001$) or inpatient treatment (N=26, 32%, versus N=54, 61%; $\chi^2=14.98$, df=1, $p<.0001$). However, they were equally likely to have been receiving some form of current treatment (N=40, 42%, versus N=45, 46%).

When symptoms were assessed, as shown in table 2, adolescents were less likely than adults to have symptoms of psychosis such as paranoia, hallucinations, or delusions. Subjective depression and aggressive behavior were common in both groups. These data are congruent with diagnoses, which are also presented in table 2. Adolescents were less likely to be given a diagnosis of psychosis or personality disorder but more likely to be diagnosed as suffering from adjustment disorders or conduct disorders. Both groups frequently suffered from substance abuse, with adolescents tending to use drugs and adults tending to use alcohol.

When urgency of need for treatment was evaluated with Rosenn's scale (9), adolescent and adult emergency room visits were rated as about equally urgent. Fifty-five percent of adolescent versus 50% of adult visits were classified as emergencies requiring immediate attention, 27% versus 21% as emergencies that required evaluation within 24 to 36 hours, 7% versus 13% as crises that required evaluation within a few days, and 11% versus 16% as pseudo-emergencies (situations in which intervention was requested but not medically warranted).

Although adolescents were more likely than adults to have had a chief complaint of suicidal acts or ideation, they were not significantly more likely to be rated as having serious suicidal tendencies (see table 3).

TABLE 2. Symptoms Reported and Diagnoses Made During 100 Adolescent and 100 Adult Visits to a Psychiatric Emergency Room

Finding	Number of Visits: Adolescent[a]	Number of Visits: Adult[a]	χ^2 (df=1)	p
Symptoms				
Hallucinations	7	21	7.02	<.01
Delusions	10	26	7.62	<.01
Drug use	30	17	4.00	<.05
Alcohol use	23	33	1.89	n.s.
Somatic complaints	15	19	0.32	n.s.
Aggressive behavior	31	24	0.90	n.s.
School problems	31	1	31.29	<.001
Mental retardation	3	4	0	n.s.
Paranoia	8	28	12.23	<.001
Anger	26	17	1.90	n.s.
Subjective depression	48	39	1.30	n.s.
Diagnoses				
Affective disorder	18	30	3.32	n.s.
Bipolar	0	5		
Major depressive	5	7		
Other	13	18		
Other psychosis	9	31	13.78	<.001
Schizophrenia	3	12		
Paranoia	1	3		
Other or unspecified	5	16		
Substance abuse	21	21	0	n.s.
Alcohol	9	17		
Other or mixed	12	4		
Personality disorder	11	27	7.31	<.01
Borderline	3	10		
Other	8	17		
Adjustment disorder	42	13	19.66	<.001
Conduct disorder	16	0	15.28	<.001
V code	7	2	1.86	n.s.
Anxiety disorder	3	7	0.95	n.s.
Other	6	8	0.08	n.s.

[a]Adolescent=13–17 years old; adult=18 or older.

TABLE 3. Severity of Suicidal Tendencies Seen During 100 Adolescent and 100 Adult Visits to a Psychiatric Emergency Room

Severity	Number of Visits: Adolescent[a]	Number of Visits: Adult[a]
None	34	45
Slight: occasional thoughts of death, e.g., "I would be better off dead"	14	8
Mild: frequent thoughts of death or occasional thoughts of suicide	4	2
Moderate: often thinks of suicide or has thought of specific method	9	4
Severe: often thinks of suicide with plan or has made suicide gesture of the communicative type	8	7
Extreme: has made preparations for a potentially serious attempt	3	2
Very extreme: suicide attempt with intent to die or with medical danger of death	1	1
No information	27	31

[a]Adolescent=13–17 years old; adult=18 or older.

Of all adolescent visits, however, 39 of 100 were rated as presenting some evidence of suicidal tendencies and 12 as presenting evidence of suicidal tendencies ranging from severe to very extreme. Adolescents also did not differ from adults in mean number of suicide

attempts: 29 of the adolescents had a history of attempts—17, a single attempt; nine, two–five attempts; and three, more than five attempts. Ratings of suicidal intent and medical seriousness of the intent did not differ between the two groups; in fact, attempts in both groups were predominantly rated as minimal to mild. Only three of the adolescents were rated as having been in moderate medical danger from suicide attempts (e.g., took 10 secobarbital sodium capsules, with brief loss of consciousness) and only one as having been in severe danger. It should be remembered, however, that adolescents with truly severe suicide attempts would most often be hospitalized immediately on the intensive care unit and not seen in the psychiatric emergency service.

Adolescents were no more likely than adults to have been restrained in the psychiatric emergency service (15 versus nine) or to have been hospitalized from the service (35 versus 29). They did, however, require more direct (face-to-face) staff time than adults (mean±SD=91.8±54.7 versus 70.5±36.4 minutes; $t=3.24$, $df=198$, $p<.005$) and more total staff time (130.6±68.61 versus 101.1±50.1 minutes; $t=3.48$, $df=198$, $p<.001$).

DISCUSSION

Adolescents using the psychiatric emergency service of an urban general hospital were predominantly middle adolescent (15 to 17 years) rather than younger. They were similar to adults seen in this setting in terms of race and sex as well as acuteness of the problem and need for hospitalization. They were also similar to adults in terms of their likelihood of being in current treatment (approximately 40%) and their likelihood of requiring restraints (approximately 15%) in the emergency room area.

Adolescent patients, however, differed significantly from adult patients in a number of important ways. Some of these, such as greater likelihood of having insurance, less likelihood of living alone, and relatively clearer precipitants, tend to make rapid emergency assessment easier. Most of the differences from adults, however, tend to make such assessment more difficult. Adolescents came from a more geographically diffuse area. They were less likely to have been seen by the service previously or to have had past treatment, and they took more time to evaluate.

Our data are consistent in indicating that adolescents present with different symptoms and receive different diagnoses than do adults. The differences in diagnoses between adolescents and adults are, however, difficult to interpret. On the basis of these retrospective findings, we cannot be sure to what extent there is an actual difference in diagnostic entities between adolescents and adults and to what extent the apparent difference is due to either different diagnostic criteria or different data-gathering techniques used by staff for the two groups.

Our findings do show that suicidal ideation or behavior is a more common chief complaint for adolescents than for adults. This study also makes clear that a need for emergency services for adolescents exists. The fact that adolescents using the service were more likely than adults to have financial resources for private care and to have come from some distance suggests that there are fewer alternative community services providing care for emergencies in adolescents than in adults. The study also suggests that emergency services need to budget more time for adolescents than for other emergencies and that, given the different presentations and symptoms of adolescents, staff need either special training or the availability of consultation when dealing with adolescent emergencies. Furthermore, the high frequency of family problems as precipitants of adolescent emergency visits highlights the need for family therapy skills in psychiatric emergency service workers.

The study also highlights the breadth of problems with which adolescents present. It suggests a subpopulation of potential young chronic patients (11), with 26 (32% of visits) having a history of past inpatient treatment, 24 (24%) having a previous psychiatric emergency service visit, 40 (42%) being in current treatment, and nearly 30 (30%) having drug abuse problems and problems with aggressive behavior.

All of these findings indicate that adolescents coming to the psychiatric emergency service have serious, acute pathology and that their evaluation and treatment pose significant problems. These problems are certainly even greater in communities that may not have either an organized psychiatric emergency service or adequate numbers of child psychiatrists or other mental health professionals trained to work with children. Given the current shortage of child psychiatrists and of child psychiatry fellows (12, 13), this is a problem that is likely to persist for some time. Presumably, adolescent emergencies occur in all communities, and each community will need to find creative ways to use existing professional resources or else develop new ones in order to provide appropriate services.

The study also raises important questions for future research. It is unclear, for example, what is the natural history of low-lethality suicide attempts by adolescents and what percentage of these patients will develop life-threatening suicide attempts, "outgrow" the behavior, or develop chronic low-lethality "suicidal" behavior—the "deliberate self-harm syndrome" (14). How many of these adolescents, with what cluster of symptoms, will have multiple hospitalizations or will become unable to function adequately as adults? It would also be useful to know more about diagnostic profiles of adolescents. Would a prospective study that used a standardized interview lead to the same differences between adolescents and adults in diagnoses in an emergency setting, or would it lead to more similar diagnostic profiles? It would also be useful to compare the characteristics of individuals with low-lethality suicidal behavior seen in this setting and those of

individuals with high-lethality suicidal behavior seen in other settings (e.g., those admitted directly to intensive care units) in order to understand better the full range of adolescent suicidal behavior. There are also important unanswered questions about the health care delivery system for adolescents; these relate to the availability of other settings in delivering care for such emergencies and the extent to which services are delivered by the community mental health system, private mental health practitioners, and pediatricians and other workers outside the specialty mental health sector.

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Life Events, Depressive Symptoms, and Immune Function

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Because both bereavement and depression have been associated with impaired immune responses, the authors studied two indicators of immune function, natural killer (NK) cell activity and measures of T cell subpopulations, in 37 women who differed in the magnitude of recent life events. Women who had experienced major life changes had lower NK cell activity than women who had few changes. Severity of depressive symptoms in these women was associated with an impairment of NK cell activity, an absolute loss of suppressor/cytotoxic cells, and an increase in the ratio of T helper to T suppressor/cytotoxic cells.

(Am J Psychiatry 1987; 144:437–441)

Considerable interest has recently been focused on changes in cell-mediated immune function that occur in persons undergoing distressing life experiences. Lymphocyte responses to mitogen stimulation have been found to be lower in bereaved men and women 2 months after the death of a spouse than in age-matched control subjects (1). In a longitudinal study (2), lymphocyte responses were found to be significantly suppressed among men whose wives had recently died. Other studies (3, 4) have found lower mitogen responses in hospitalized patients with major depressive disorder.

Presented in part at the American College of Neuropsychopharmacology, Maui, Hawaii, 1985, and the 139th annual meeting of the American Psychiatric Association, Washington, D.C., May 10–16, 1986. Received Oct. 21, 1985; revised April 11 and Oct. 31, 1986; accepted Dec. 29, 1986. From the Department of Psychiatry, University of California, San Diego; the Alcohol Research Center, San Diego Veterans Administration (VA) Medical Center; the Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles; and the Geriatric Research, Education, and Clinical Center, West Los Angeles Veterans Administration Medical Center. Address reprint requests to Dr. Irwin, Psychiatry Service (116A), VAMC, 3350 La Jolla Village Dr., San Diego, CA 92161.

Supported by Biomedical Research Support grant RR-05756 and grant CA-30187 from the Division of Extramural Activities, National Cancer Institute.

The authors thank Dr. Edward L. Korn for statistical advice, Dr. T. Makinodan for critical review of the paper, the Hematology-Oncology Service of the West Los Angeles VA Medical Center, the West Los Angeles VA Hospice, Jane Babbitt for technical help, and Dr. L.J. West.

Investigation of two other indicators of immune function, natural killer (NK) cell activity and measures of T cell subpopulations, could extend these earlier observations and further clarify the effect of psychological processes on immune function. Subpopulations of T cells help regulate the immune response, especially antibody formation (5). For example, the absolute number of T helper (Th) cells is deficient in acquired immune deficiency syndrome (AIDS) (6), and a lower percentage of Th cells has been described in association with a number of infectious diseases (7). The T suppressor/cytotoxic cells (Ts) down-regulate the production of antibodies (5), and a decrease in their numbers is associated with an increase in autoantibodies (8). Natural killer cells are cytolytic cells that are considered important in the immunological surveillance of virus-infected and tumor cells (9).

Although the regulation of NK cell activity is complex, psychological stresses appear to have a role (10). Impairment of NK cell activity has been reported in depressed, anxious, and lonely persons (11–13) and has been related to depressive symptoms in a longitudinal study of bereaved women (14). However, the relationship between life changes and NK cell activity remains controversial (11, 13). To our knowledge, whether the absolute and/or relative numbers of Th or Ts cells are affected by major life changes or are related to depressive symptoms has not been evaluated.

In this study, measures of NK cell activity and T cell subpopulations were compared among groups of women who differed in the magnitude of recently experienced life changes. The relationship between the severity of depressive symptoms and alterations in these immunological measures was also examined.

METHOD

This cross-sectional study was designed to evaluate the relationship between life events and measures of immune function. We originally studied 45 women identified to provide different experiences of recent life events; they came from three groups. First were women whose husbands were undergoing medical treatment in the Hematology-Oncology Service of the West Los Angeles Veterans Administration (VA) Medical Center for recently (less than 6 months ago) diagnosed metastatic lung cancer. (In a separate fol-

low-up study, we found that these women's husbands died 1 to 7 months after this evaluation.) Second were women whose husbands had died of lung cancer in the previous 1 to 6 months. Third were women employed by the University of California or the VA whose husbands were in good health. Women from these groups were excluded if they had a history of any chronic medical disorder associated with altered immune function, a recent episode of infectious disease, use of drugs known to affect immune function, and/or abuse of alcohol or other substances. Six of the original 45 subjects were excluded because they had chronic diseases, and two others were dropped because of recurrent acute viral infections.

The 37 women who made up the study population had a mean age of 59.3 years (range, 40 to 71 years) and were in the middle range of socioeconomic status. Thirty-one of the subjects were white, and six were black. Only two subjects smoked tobacco. All subjects were weighed at each visit; none reported major changes in weight in the month before the study.

All subjects were evaluated on multiple occasions over a 1–3-month period. On the basis of availability for testing (reflecting how far the subjects lived from the hospital), 18 of the 37 subjects were tested three times; 14, four to five times; and five, six or more times. At each testing, blood was drawn at approximately the same hour to control for circadian effects. The subject then met with a psychiatrist who assessed current (within the past 6 months) changes in the spousal relationship (i.e., illness or death of the spouse) and other life experiences during the previous 2 weeks using the Social Readjustment Rating Scale (15). Recent changes in health status and medication and alcohol use were evaluated, and depressive symptoms were rated by using the Hamilton Rating Scale for Depression (16).

Total WBC and differential cell counts were obtained by standard techniques. Peripheral blood lymphocytes were isolated by sedimentation over ficoll-hypaque (Ficoll-Paque, Pharmacia, Piscataway, N.J.) followed by treatment with carbonyl iron (17). This procedure yields a cell suspension that typically contains 95% lymphocytes (18). The isolated cells were more than 99% viable (by trypan blue exclusion). The medium used for suspending the cells throughout the assay was RPMI-1640, containing 10% fetal bovine serum (Sterile Systems, Logan, Utah), 1% L-glutamine, and 0.1% gentamicin.

Natural killer cell activity was measured in a standard 4-hour chromium release assay that was performed in 0.2 ml volumes in U-bottom microplates (18). Cell populations were titrated for cytolytic activity against 5,000 51-chromium-labeled K562 target cells. Effector cell suspensions were adjusted to 2×10^6 cells/ml, and effector-to-target cell ratios of 40:1, 20:1, 10:1, and 5:1 were tested in triplicate. Plates were centrifuged for 2 minutes at 500 *g* before incubation for 4 hours at 37°C in 5% CO_2 and again before harvesting of 100 μl of supernatant from each well. Radioactivity in the supernatant was determined by a gamma counter, and the percentage of 51-chromium released in each effector-to-target cell ratio was calculated by using the following formula:

$$\%\ 51\text{-chromium release} = \frac{\text{CPM experimental} - \text{CPM SR}}{\text{CPM TR} - \text{CPM SR}},$$

where *CPM* equals counts per minute, *SR* equals spontaneous release (target cells and medium), and *TR* equals total release (target cells and 1 N HCl) (18). The percentage of spontaneous release was less than 10% in all experiments.

Data are presented as the number of lytic units in 10^6 cells. Lytic unit values reflect the relative cytotoxicity of the lymphocyte preparations and are more accurate than comparative chromium release data, which may be influenced by the percent of lysis (19). Lytic units were obtained by fitting scale families of curves to our data (17). In this case, each curve was fit separately to the modified exponential family of equations. One lytic unit was defined as the number of effector cells killing 20% of the target cells.

T lymphocyte subpopulations were enumerated by direct immunofluorescence by using monoclonal antibodies Leu-3 and Leu-2 (Becton Dickinson, Mountain View, Calif.). Leu-3 has been identified on Th and Leu-2 on Ts. For each sample, 2×10^6 cells/ml were suspended in phosphate-buffered saline without calcium or magnesium and containing 0.1% sodium azide. The monoclonal reagent was added and incubated with the cell suspension on ice for 15 minutes. Cells were washed twice with phosphate-buffered saline and resuspended at a concentration of 4×10^6 cells/ml. The smears were examined with a Zeiss fluorescent microscope equipped with a mercury light source and epifluorescence. The percentage of positive-staining lymphocytes was determined by counting a minimum of 200 lymphocytes. The relative numbers of T lymphocytes and of Th (Leu-3 positive) and Ts (Leu-2 positive) cells were determined as a percentage of the total lymphocyte population. Because of technical problems in the enumeration of T lymphocyte subpopulations, multiple measures of these immune measures were obtained in 28 of the 37 subjects.

To minimize the influence of variability in the immune measures, assays of the immune measures of total lymphocyte counts, percent of Th, percent of Ts, ratio of Th to Ts, and NK activity were repeated at each of the assessment intervals, and results were expressed as a mean±SE for individual subjects. Scores on the Social Readjustment Rating Scale and Hamilton depression scale obtained from each testing were expressed as means±SD. On the basis of their overall mean Social Readjustment Rating Scale scores, the 37 subjects were divided into three groups: 13 women with low scores (54 or less), 12 with moderate scores (55 to 99), and 12 with high scores (100 or more). To test for group differences on the dependent variables such as age, depressive symptoms (Hamilton depres-

TABLE 1. Age, Race, Depression Score, and Immune Variables of Women With Low, Moderate, and High Social Readjustment Rating Scale Scores[a]

Measure	Group, by Social Readjustment Rating Scale Score						ANOVA	
	Low (N=13)		Moderate (N=12)		High (N=12)		F	
	Mean	SD	Mean	SD	Mean	SD	(df=2,34)	p
Social Readjustment Rating Scale score	31.9	16.4	81.7	11.1	126.6	24.7	84.4	<.001
Age (years)	54.8	9.5	55.3	6.3	57.8	9.4	—	n.s.
Race[b]	0.7	0.2	0.8	0.2	0.8	0.2	—	n.s.
Number of blood samples	3.6	0.6	3.8	0.9	3.8	0.9	—	n.s.
Hamilton depression score	5.3	5.2	14.7	7.5	12.0	6.8	6.8	<.003
Natural killer cell activity (lytic units)	40.2	25.7	15.6	6.4	18.1	10.0	8.3	<.001
Absolute number of lymphocytes (cells/ml × 10)	1.8	0.5	2.2	0.5	2.5	0.8	—	n.s.
Percent of Th cells[c]	34.0	6.5	38.0	9.8	37.0	8.4	—	n.s.
Percent of Ts cells[c]	27.0	8.7	23.0	8.4	26.0	8.5	—	n.s.
Th-to-Ts ratio[c]	1.6	0.6	2.0	0.6	1.6	0.4	—	n.s.

[a]Low=54 or less; moderate=55–99; high=100 or more.
[b]0=black; 1=white.
[c]N=9 in low-score group; N=9 in moderate-score group; N=10 in high-score group.

sion scale scores), and the immune measures, one-way analyses of variance were run, followed by multiple range tests using Student and Newman-Keuls procedures for comparisons among groups. The relation between depressive symptoms and the immune variables was explored by using Pearson correlations.

RESULTS

Mean Social Readjustment Rating Scale scores were significantly different among the three groups (table 1) ($F=84.4$, $df=2, 34$, $p<.001$), and multiple range tests confirmed that each group was different from each of the other two ($p<.05$). Eight of the 11 women whose husbands were healthy were classified in the low-score group, three of these women had moderate scores, and none had high scores. However, two of the 16 women who were anticipating the death of their husbands had high scores, nine of these women had moderate scores, and five had low scores. All 10 of the women who had experienced the death of their husbands had high scores. The difference among these groups was significant ($\chi^2=33.7$, $df=4$, $p<.001$).

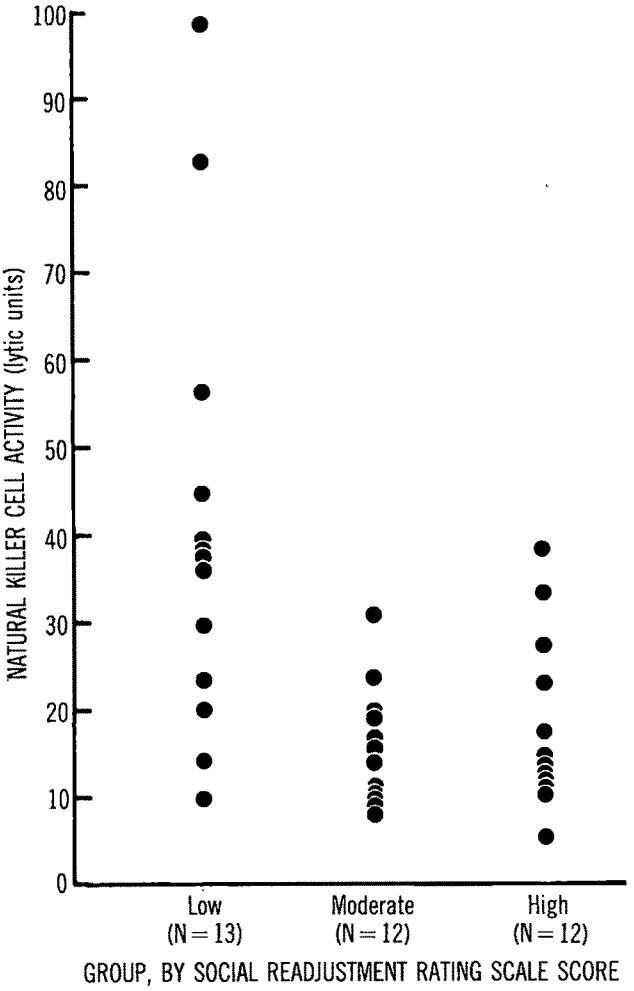
Women with low, moderate, or high Social Readjustment Rating Scale scores did not differ from each other in mean age, ethnic group, or mean number of blood samples (table 1).

Hamilton depression scale scores were significantly different among the three groups (table 1): the groups with moderate and high Social Readjustment Rating Scale scores had significantly greater mean Hamilton scale scores than the group with low Social Readjustment Rating Scale scores ($p<.05$). Mean Hamilton scale scores were not different for the groups with moderate and high Social Readjustment Rating Scale scores. Natural killer cell activity was also significantly different among the three groups (table 1 and figure 1). The groups with moderate and high Social Readjustment Rating Scale scores had significantly lower NK cell activity than did the group with low Social Readjustment Rating Scale scores ($p<.05$), but NK cell activity was not different between the groups with moderate and high scores. Neither the absolute number of lymphocytes nor T cell subpopulations, including the variables of percent of Th, percent of Ts, and the ratio of Th to Ts, were different among the groups (table 1).

To investigate the relationship between the intensity of depressive symptoms and alterations in the immune variables, mean total scores on the Hamilton depression scale of individual subjects were correlated with mean immune function values. Reduced NK activity was related to the Hamilton scale total score ($r=.28$, $N=37$, $p<.05$) and also with the Hamilton subscales of depressed mood ($r=.39$, $N=37$, $p<.01$) and insomnia ($r=.28$, $N=37$, $p<.04$). The remaining subscales—anxiety and somatic symptoms—did not yield significant correlations. Figure 2 depicts the relationship between Hamilton depression scale total scores and the ratio of Th to Ts. An increase in the ratio of Th to Ts was correlated with mean Hamilton scale total scores ($r=.54$, $N=28$, $p<.002$) and with the subscales of depressed mood ($r=.45$, $N=28$, $p<.005$), insomnia ($r=.43$, $N=28$, $p<.01$), and anxiety ($r=.63$, $N=28$, $p<.001$). Finally, mean Hamilton scale total scores were associated with an absolute loss of Ts ($r=.42$, $N=28$, $p<.01$) but were not related to value of Th or total lymphocyte counts. The number of blood samples was not related to Hamilton scale scores or to any immune measure.

Several additional analyses were carried out to characterize the attributes of the 28 subjects for whom T cell subpopulations were obtained and to further clarify the relationship between the ratio of Th to Ts and Hamilton scale scores. The distribution of Hamilton scale scores appeared bimodal; the sample of 28 women was split at the median Hamilton scale score.

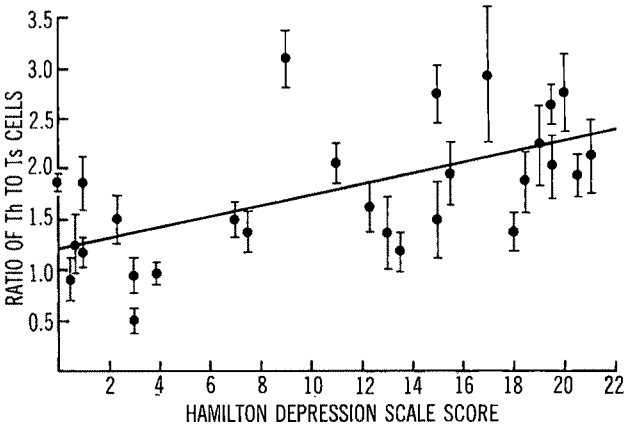
FIGURE 1. Natural Killer Cell Activity in Women With Low, Moderate, and High Social Readjustment Rating Scale Scores[a]



[a]Low=54 or less; moderate=55–99; high=100 or more. Each point represents the individual mean of multiple measures.

In women with high Hamilton scale scores, the mean± SD Th-to-Ts ratio (2.0±0.6) was significantly greater than the mean ratio (1.5±0.6) in the women with low Hamilton scale scores (t=2.3, df=26, p<.03). Variance of multiple measures of the Th-to-Ts ratio was not significantly different between the groups with high and low Hamilton scale scores (F=1.2, df=1,26, p<.75), and plots of the Th-to-Ts ratios and Hamilton scale scores obtained on the same day did not demonstrate a relationship between day-to-day variation in the ratio of Th to Ts and variability in the subjects' Hamilton scale scores. In addition to the difference in the ratio of Th to Ts between the Hamilton scale groups, mean±SD NK cell activity (16.5±8.0 lytic units) in the groups with high Hamilton scale scores was significantly lower than the mean value (36.2± 27.0 lytic units) in the group with low Hamilton scale scores (t=2.6, df=26, p<.02). Neither T lymphocyte counts, mean age, ethnic composition, nor number of blood samples differed between the two groups.

FIGURE 2. Relationship Between Ratio of T Helper (Th) to T Suppressor/Cytotoxic (Ts) Cells and Hamilton Depression Scale Scores in 28 Women[a]



[a]Each point represents the mean±SEM of multiple measures of the ratio of Th to Ts in an individual subject; y=0.47x+1.21, r=.54, N=28, p<.002.

DISCUSSION

This study demonstrates that NK cell activity was significantly lower in women undergoing major life changes such as bereavement than in subjects who were similar in age and sociodemographic characteristics but who had few such life changes. Severity of depressive symptoms was correlated with impaired NK cell activity, a lower number of suppressor/cytotoxic cells, and a higher ratio of helper to suppressor/cytotoxic cells. In spite of daily variations in NK cell activity and T cell subpopulations, multiple measures at different times confirmed the reproducibility of the determinations and provided a mean measure to minimize the influence of this variability.

These changes in the number of Ts and in the ratio of Th to Ts were within the normal range and do not necessarily have clinical significance. However, others have reported that autoantibodies occur more often in clinically depressed patients than in control subjects (20–23) and that lower Ts is associated with the emergence of autoantibodies (8).

Although the patterns of changes in immune function in this study were related to the intensity of depressive symptoms, our findings do not necessarily generalize to patients suffering from major depressive disorders. We evaluated subjects who were undergoing major life changes, with associated dysphoric mood, insomnia, somatic symptoms, and anxiety. We did not undertake extensive diagnostic assessment of depressive disorders.

The association between depressive symptoms and impaired NK cell activity is in accord with the findings of others (11, 12). We also controlled for the use of tobacco, alcohol, and medications; excluded subjects with chronic and acute medical disorders; evaluated potential weight changes; and rated depressive symp-

toms by clinical observations rather than by self-report.

The relative contribution of adverse life events and of depressive symptoms to changes in NK cell activity and Th-to-Ts ratios is difficult to determine from our data. However, the effects of depressive symptoms on immune function may be relatively more important than effects associated with life events. Changes in T cell subpopulations were related to depressive symptoms but not to group differences in the magnitude of life events. In another study (14) we followed bereaved women and demonstrated that changes in the severity of depressive symptoms, but not the occurrence of the actual bereavement event, were associated with impaired NK cell function. Locke et al. (11) also reported that lower cytotoxic activity was predicted by psychiatric symptoms but not by retrospective report of life change.

This study was conducted to evaluate the relationship between distressing life changes and alterations in measures of immune function. Thus, no data were generated on possible mechanisms underlying our results. However, a variety of neurohormones and neurotransmitters could mediate the reduction of NK cell activity during bereavement. Cortisol and norepinephrine, both of which are often higher in the plasma of persons undergoing distressing life experiences (24), suppress NK cell activity in vitro (25, 26). In animal studies, the central administration of corticotropin-releasing factor coordinates the release of catecholamines (27), adrenocorticotrophic hormone, and β-endorphin (28) and acutely suppresses rat splenic NK cell activity (29). Finally, one study (30) demonstrated that opiate peptides mediate the immunosuppressive effects of stress in the rat.

In conclusion, we found that women who experienced losses and distressing life changes showed lower NK cell activity than women with few life events. The severity of their depressive symptoms correlated with an impairment of NK cell activity and with alterations in T cell subpopulations. These results represent an advance in our understanding of the neuromodulation of immune function.

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A Study of Crying in Medically and Surgically Hospitalized Patients

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In a prospective study of hospitalized patients referred to a psychiatry consultation service, 46 patients were referred for a presumed diagnosis of depression because crying was a prominent symptom. Psychiatric consultation determined that 20% had a psychiatric disorder only, 33% had a neurological disorder only, 43% had both psychiatric and neurological disorders, and 4% had a previously undescribed entity, "essential" crying. The most common neurological disorder in these crying patients was bilateral hemispheric dysfunction associated with dementia or delirium; the most common psychiatric disorder was major depression. Effective therapy for patients who cry depends on proper identification of the cause of crying.
(Am J Psychiatry 1987; 144:442–447)

Over the past decade our psychiatry consultation service has received numerous requests to see patients because of crying. Depressive illness or at least discouragement was assumed to be the reason for the crying. However, we often found the patients' crying to be due to the presence of neurological disease, which was vastly underestimated by the referring physicians.

The standard textbook example of crying due to neurological illness is pseudobulbar palsy (1). The crying in these cases is commonly referred to as "pathological" and is most often caused by bilateral corticobulbar tract lesions. However, both bilateral and unilateral cortical and/or subcortical lesions and degenerative diseases have been reported to cause pathological crying without pseudobulbar palsy (2). In addition, in dacrystic epilepsy (3), a rare disorder, crying is the ictal event.

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The authors thank Drs. Elliot Ross and George Vaillant for their contributions to the paper.

Of further interest is an observation by Poeck (4) that pathological crying often has distinctive motor qualities. It is usually very abrupt in onset, and each episode appears quite similar to the next; that is, for a given patient there is stereotypy in the grimacing, sobbing, and other motor manifestations of crying. Further, the crying tends to be out of keeping with the prevailing mood of the crier and the environmental stimuli. Thus, it might be possible to distinguish crying due to neurological disease from that due to psychiatric disease merely through careful observation of the crying episodes.

We carried out an 18-month prospective study of all patients referred to our psychiatric consultation service. From this population, patients who were referred because of crying became the principal subjects of the study.

The study tested the following five hypotheses. 1) Crying behavior is a frequent indication for psychiatric consultation for presumed depressive or adjustment disorder. 2) Many crying patients suffer from structural or metabolic brain dysfunction and not from a primary psychiatric disorder. 3) When crying is due to neurological disease, bilateral cerebral disease is the most common cause. 4) There are observable characteristics of crying that distinguish crying due to neurological disorders from crying due to psychiatric disorders. 5) Among patients referred for psychiatric consultation, the proportions of patients with psychiatric and neurological diagnoses are similar for those who cry and those who do not cry.

METHOD

The Veterans Administration Hospital in White River Junction, Vt., has 204 acute medical and surgical beds and a 40-bed rehabilitation unit. Most patients (98%) are male, and all are over 18 years of age.

The psychiatric consultation service receives referrals of 175–250 patients a year from medical and surgical house staff. Patients are assessed by chart review, interview, and, when possible, information obtained from family members. Patients are followed during hospitalization and are usually seen 1 month after hospitalization, at the time of medical or surgical follow-up.

From July 1, 1980, through Dec. 31, 1981, we systematically recorded the following data for all patients referred for psychiatric consultation: reason for referral, sex, age, cognitive and neurological examination findings, results of brain laboratory studies, and major medical, neurological, and psychiatric diagnoses. Psychiatric diagnoses were made according to *DSM-III* criteria, and medical and neurological diagnoses followed *ICD-9-CM* guidelines. We gave all patients a bedside comprehensive cognitive examination that has been used by the service for several years (available on request). The study was naturalistic in that patients had specialized evaluations such as EEGs and CAT scans only when these were clinically indicated. A neurologist (J.L.B.) reviewed all cases with respect to neurological diagnoses.

In all cases the referring physician filled out a consultation request form that specified the reason for referral. In addition, we always asked the physician personally whether the patient had been informed of the referral and requested more complete information on the reasons for referral. All patients referred because of crying became the principal study subjects, after giving informed consent. We should note that in some cases the request for consultation specifically mentioned excessive crying. In other cases the request referred only to suspected depression, but when we questioned the referring physician, crying was the major reason depression was suspected and thus was the major reason for the referral.

Of all the patients we evaluated in the study period, those who cried were divided into two groups: 1) "prominent criers"—if they were referred because of crying, crying dominated the recent history, and crying was present on repeated psychiatric evaluations—and 2) "nonprominent criers"—if crying occupied a minor part of the recent history and was minimally present in the course of bedside psychiatric evaluation. Patients in this group had not been referred for crying.

A detailed evaluation of the crying was performed, with identification of each of the following characteristics. These data represented the subjective experience of the patients and characteristics of the crying observed by us.

Stimulus characteristics that we recorded included 1) the meaning or emotional significance of the stimulus to the patient and 2) whether it was internally generated (thoughts, feelings) or externally generated (events).

Response characteristics that we observed included 1) whether the crying was appropriate to the stimulus or dissociated (inappropriate to the stimulus), 2) whether the onset of crying was "push-button" in character (abrupt onset) or gradual, and 3) whether the crying was stereotyped (crying episodes identical in appearance from one episode to the next) or variable. An example of stereotyped crying is when each episode displays the same grimace, sobbing, and other characteristics.

Psychiatric consultations, including the evaluations of the crying, were done first by the psychiatry resident on the consultation service and then independently by the staff psychiatrist. Evaluations of crying were repeated when possible as we followed the patients throughout their hospital stay.

TABLE 1. Diagnoses of 46 Hospitalized Medical and Surgical Patients With Prominent Crying

Diagnosis	N	%
Psychiatric disorder only	9	20
Psychiatric disorder plus medical/neurological disorder[a]	20	43
Neurological disorder only[a]	15	33
"Essential" crying	2	4

[a]Excluding spinal cord and peripheral nervous system disorders.

Diagnoses of depressive disorder were made for patients with neurological dysfunction if they met *DSM-III* criteria for a depressive disorder. When patients only partially met the criteria, we queried the nursing staff and the family for any biological depressive signs and/or any maladaptive behavior not consonant with the usual course of recovery from brain insults. Care was taken to note any aphasias, agnosias, apraxias, and aprosodias. The importance of these factors in assessing depression in patients with neurological dysfunction has been stressed by Ross and Rush (5), Gans (6), Robins (7), Robinson and Price (8), and Charatan and Fisk (9).

All medical records of criers were reviewed 1–2 years after the index consultation to identify new medical, neurological, or psychiatric developments.

RESULTS

Two hundred ninety-six consultations were done for 276 consecutively referred patients. Forty-six (17%) of these patients were prominent criers and 17 (6%) were nonprominent criers. The mean age of the prominent criers was 56.7 years; the median age was 60 years. Forty-four (96%) of these 46 patients were men.

Table 1 shows that only a minority of the prominent criers had psychiatric disorders alone. Of these nine patients, three had major depression, one had atypical depression, two had an anxiety disorder, and three had adjustment disorders. The majority of the prominent criers had a psychiatric disorder plus a medical or neurological condition that did or could in theory contribute to a tendency to cry easily, for example, patients withdrawing from alcohol or taking steroids. The precise effects of these conditions on the expression of emotions are unknown but may be important. Fifteen prominent criers had neurological disorders (excluding spinal cord and peripheral nervous systems disorders) and no discernible psychiatric disorders. Two cases designated "essential" crying were patients for whom easy crying was a longstanding personality trait. These two patients had no evidence of neurological or psychiatric disorder and are discussed at greater

TABLE 2. Psychiatric Disorder Plus Medical/Neurological Disorder in 20 Patients With Prominent Crying

Psychiatric Disorder	Medical/Neurological Disorder	Number of Patients
Major depression	Dementia[a]	3
Major depression	Delirium	1
Major depression	Cerebrovascular dementia	1
Major depression	Dementia and alcohol withdrawal[b]	1
Major depression	Delirium and dementia	1
Major depression	Cerebrovascular disease	2
Major depression	Complex partial seizures	2
Major depression	Complex partial seizures, thyroid nodule, steroid treatment	1
Major depression	Steroid treatment	1
Adjustment disorder with depressed mood	Dementia and alcohol withdrawal	1
Adjustment disorder with depressed mood	Cerebrovascular dementia	1
Adjustment disorder with depressed mood	Cerebrovascular disease and dementia	1
Adjustment disorder with depressed mood	Multiple sclerosis and delirium	1
Adjustment disorder with anxious mood	Alcohol withdrawal	2
Adjustment disorder with mixed emotional features	Cerebrovascular dementia	1

[a]Dementia refers to the primary degenerative type unless otherwise indicated.
[b]"Alcohol withdrawal" indicates patients who were withdrawing from alcohol use but were not in delirium tremens unless so specified.

TABLE 3. Type of Neurological Disorder in 15 Patients With Prominent Crying Who Had a Neurological Disorder Only

Neurological Disorder	Number of Patients
Cerebrovascular dementia with pseudobulbar palsy, delirium, and steroid treatment	1
Cerebrovascular disease	2
Delirium	5
Delirium, cerebrovascular disease, and dementia[a]	1
Delirium and dementia	1
Bilateral brainstem infarction with pseudobulbar palsy, delirium, and dementia	1
Complex partial seizures, cerebrovascular disease, and delirium and/or dementia	1
Delirium (drug induced) and alcohol withdrawal[b]	2
Multiple sclerosis	1

[a]Dementia refers to the primary degenerative type unless otherwise indicated.
[b]"Alcohol withdrawal" indicates patients who were withdrawing from alcohol use but were not in delirium tremens unless so specified.

length in the Discussion section. (An appendix giving all clinical data in detail is available on request.)

Table 2 displays the combinations of psychiatric and neurological diagnoses in patients who had both kinds of disorders, and table 3 lists the diagnoses of the patients with neurological disorders only. In all of the prominent criers, major depression was the most common psychiatric diagnosis. Inspection of tables 2 and 3 reveals that bilateral cerebral disease of various etiologies was the most common neurological problem. There were only two cases of pseudobulbar palsy.

TABLE 4. Crying Characteristics of 46 Patients With Prominent Crying

Diagnostic Category and Type of Crying[a]	Number of Patients
Psychiatric disorder only (N=9)	
Appropriate	8
Appropriate and push-button	1
Psychiatric disorder plus medical/neurological disorder (N=20)	
Appropriate	13
Appropriate and push-button	4
Dissociated and push-button	3
Neurological disorder only (N=15)	
Appropriate	0
Appropriate and push-button	3
Appropriate, push-button, stereotyped	1
Dissociated and push-button	2
Dissociated, push-button, stereotyped	7
Dissociated	2
Essential crying (N=2)	
Appropriate and push-button	2

[a]Terms are defined in text.

Table 4 displays the crying attributes of the 46 prominent criers. We constructed chi-square tables for the patients with psychiatric disorders only and those with neurological disorders only to compare crying characteristics with diagnostic groups. For this analysis we omitted the patients with both kinds of disorders because of the difficulty in knowing the relative contributions of psychiatric and neurological disorders to crying, and we omitted the essential criers because there were no data germane to the hypothesis tested. We found that, compared to the crying of patients with psychiatric disorders only, the crying of patients with neurological disorders only was more likely to be dissociated ($\chi^2=9.41$, df=1, $p<.01$, with Yates' correction), push-button ($\chi^2=10.29$, df=1, $p<.01$, with Yates' correction), and stereotyped ($\chi^2=5.00$, df=1, $p<.05$, with Yates' correction).

Table 5 presents a comparison of diagnoses for noncriers, nonprominent criers, and prominent criers. We constructed a 2×2 table to compare psychiatric disorders only and neurological disorders only in noncriers and prominent criers and computed a chi-square from these data. Prominent criers were far less likely than noncriers to have psychiatric disorders only and far more likely to have neurological disorders only. Data from the nonprominent criers showed results similar to those of the prominent criers.

DISCUSSION

We confirmed the first hypothesis: that crying constitutes a common reason for psychiatric referral of medically and surgically hospitalized patients. We are

TABLE 5. Distribution of Diagnoses for 296 Consultations on Medical and Surgical Patients

Diagnosis	Noncriers (N=233)		Nonprominent Criers (N=17)		Prominent Criers (N=46)		Total (N=296)	
	N	%	N	%	N	%	N	%
Psychiatric disorder only	148	64[a]	9	53	9	20[a]	166	56
Psychiatric disorder plus neurological disorder[b]	29	12	2	12	20	44	51	17
Neurological disorder only[b]	50	22[a]	4	24	15	33[a]	69	23
No psychiatric or neurological disorder	6	2	2	11	2	3[c]	10	4

[a]Significant difference between psychiatric disorders only and neurological disorders only in noncriers versus prominent criers ($\chi^2=14.34$, df=1, $p<.001$).
[b]Excluding spinal cord and peripheral nervous system disorders.
[c]Essential criers.

unaware of any other reports on the rate of crying in hospitalized patients with which to compare the 17% rate that we found. In carrying out the study, we were careful not to draw our medical and surgical colleagues' attention to our interest in crying, so it is possible that many patients who cried were not referred. Thus, our data do not provide clues to the absolute frequency of crying in veterans who are hospitalized.

We also confirmed the second hypothesis: that many crying patients suffer from structural or metabolic brain dysfunction and not from a primary psychiatric disorder. In fact, neurological disorders were more likely than psychiatric disorders to produce crying. If psychiatric illness is present, depressive disorders or adjustment disorders with depressed mood are likely diagnoses. This hypothesis might be further strengthened by the possibility that there were also some false negatives for early mild dementias when bedside cognitive testing was unrevealing and no laboratory studies of the brain were obtained.

We next confirmed the hypothesis that bilateral cerebral disease is the most common neurological cause of crying. Since the original account of the neuroanatomy of "pathological" crying by Wilson (2), it has been held that bilateral corticobulbar tract lesions are necessary determinants of pathological crying. The corticobulbar tracts subserve a voluntary cortical pathway to inhibit limbic and hypothalamic input to the brainstem motor nuclei controlling the various motor aspects of crying. With bilateral corticobulbar tract lesions, crying can be provoked by minor emotional stimuli or even by emotionally neutral auditory stimuli (a slammed door, for example). Pseudobulbar palsy resulting from bilateral corticobulbar lesions from strokes, motor neuron disease, multiple sclerosis, and other disorders is the classic syndrome in which pathological crying is seen. In our series, only two of the crying patients had pseudobulbar palsy. The majority had bilateral cerebral hemispheric disease with a wide variety of neuropathological entities.

Bilateral cerebral disease is not the only cause of pathological crying, however. Ross and Rush (5) demonstrated pathological crying in some patients with only right unilateral inferior frontal hemispheric lesions. These patients were all depressed, and Ross and Rush hypothesized that the pathological crying may have been a marker for depressive disease in these patients.

We confirmed our fourth hypothesis: that there are observable characteristics of crying which distinguish crying due to psychiatric disorders from that due to neurological disorders. Dissociated crying occurred more commonly in the neurological disorder group and appropriate crying more commonly in the psychiatric disorder group. In addition, there was a high rate of push-button, stereotyped crying patterns in patients who exhibited dissociated crying. Thus, it appears that certain characteristics of crying can reveal clues to the etiology of crying in a given patient.

Two cautionary notes are necessary. First, our observations of the characteristics of crying were not made blind to patients' diagnoses. Second, we did not conduct a formal interrater reliability study of our agreement on assessments of these characteristics. However, we witnessed several crying episodes of almost every patient, and in nearly all instances we were able to reach agreement on the gross characteristics of the crying: whether the onset of each episode was sudden, whether it was appropriate to the context, and whether repeated episodes were similar in appearance. A blind experiment and an interrater reliability study would be necessary to test fully this fourth hypothesis.

Our final hypothesis was that the frequencies of neurological and psychiatric diagnoses in noncriers would be similar to those of criers, as there was no reason to believe otherwise. However, psychiatric illness in the absence of CNS disease was more common in the noncriers. This observation calls into question the common assumption that crying strongly suggests psychiatric illness. The fact that nearly all patients at this hospital are male precludes conclusions about the diagnostic significance of crying in hospitalized women. Additionally, our population consisted of veterans—generally older patients—and thus the results may not be generalizable to all other hospitalized patients.

In summary, we confirmed that crying is a common indication for psychiatric referral, is frequently due to bilateral cerebral hemispheric disease, and may betray

its cause by the context in which it occurs and the nature of its motor expression.

Several other points merit discussion. The first is definitional. Conventionally, the crying that occurs in pseudobulbar palsy and other neurological conditions has been referred to as "pathological" crying. The pathological aspects are that it often occurs out of context—usually suddenly—and that it is out of the patient's control. The crying experienced by our neurologically ill group frequently met these criteria. In some cases, however, the crying was appropriate to the context. Thus, the crying which is produced by neurological disorders does not always appear to be pathological.

The term "emotional lability" has also been used frequently in describing patients who cry (or display other emotions) easily and suddenly. We could find no source of formal definition for this term. It does not necessarily appear to imply that the displayed emotions occur out of context, and it has been applied equally to patients with psychiatric and patients with neurological disorders. It has also been used to describe the unpredictable changes in mood that may occur in patients with frontal lobe damage. These mood changes may persist for hours or days and may involve a number of emotions, such as sadness with or without crying, happiness with or without laughing, and irritability. Therefore, because of the rather nonspecific nature of the term "emotional lability," we have avoided its use in our discussions.

We found two patients with a previously undescribed entity that we named "essential" crying. These men reported lifelong abrupt outbursts of crying, with tears, that occurred several times a day, usually in a context appropriate to internal and environmental cues (examples of stimuli are thoughts of home or family). They described their mood during the crying bouts as sad. The bouts were embarrassing to both patients. These men came to our attention incidentally; they happened to be in the hospital, knew that psychiatric consultation was available, and were troubled by the crying and curious about its significance. Clinical assessment revealed no psychiatric or medical/neurological contributing factors. One of the patients reported that his father, brother, paternal uncle, and three daughters had the same trait. In his family the trait was regarded as both a joke and an embarrassment.

Cultural influences on crying in our study sample should be mentioned. Almost all of our patients were rural second-, third-, or fourth-generation New Englanders. The cultural bias in this group is against men who cry. In this respect they were similar to Zborowski's (10) "Old American" subgroup of male veterans, whom he studied for pain behavior. He found that Old Americans cried in response to pain far less often than subjects of Italian and Jewish backgrounds. Thus, the effect of cultural influences on our patients was to diminish the likelihood of crying as a presenting complaint. This highlights the potency of cerebral disease in producing crying in our study patients. It should be pointed out, however, that cultural influences in other groups, such as younger women of various ethnic backgrounds, might result in heightened crying behavior in the absence of neurological disease.

We conclude with recommendations for evaluation of the patient in whom crying is a major symptom. Since proper therapeutic intervention will depend on accurate determination of the cause of the crying, a systematic diagnostic evaluation is necessary, including the patient's history, examination, and laboratory studies.

It is important to avoid any a priori assumptions about the crying, such as thinking that sadness is understandable and natural given the patient's circumstances. The history should include inquiries into the context of the crying episodes, the mood at the time of crying, the patient's premorbid crying behavior, and the presence of symptoms of affective or neurological disorder.

A complete neurological and mental status examination should be performed, with special emphasis on the cognitive examination, and several crying episodes should be observed to see whether the crying is appropriate to the context, how abrupt it is in onset, and how stereotyped the episodes are.

If the history and reexamination point to neurological disease, and if crying is a departure from premorbid functioning, abrupt in onset, stereotyped, and inappropriate to the context, then, depending on these and other clinical findings, further neurological diagnostic tests such as EEG, CAT scan, or lumbar puncture may be indicated. Such patients should be referred for neurological consultation to define the extent of appropriate investigation.

If a psychiatric diagnosis proves most likely, appropriate psychiatric intervention is indicated. If crying is due solely or partly to a neurological disorder, we have found that certain cautions are advisable. Patients whose crying is attributable to neurological dysfunction are often embarrassed by the episodes. Attempts to urge them to discuss what must be upsetting them often lead to more tears and embarrassment. A clear explanation that the crying is an expected symptom of the neurological problem and that the most reasonable strategy is to distract oneself often proves reassuring to the patient and his or her family. Psychotropic drugs may also have a role in reducing the frequency of pathological crying bouts (11–13). In our experience, cautious use of antidepressants is effective in reducing the crying episodes of certain patients, such as poststroke patients, but these agents are to be avoided in certain other patients, particularly those with delirium.

There are also patients whose crying reflects both psychiatric and neurological problems. Here the task is more difficult, requiring the physician to be sensitive to what may be distressing the patient but at the same time not to provoke excessive crying.

CONCLUSIONS

Crying is a ubiquitous human behavior that can be a symptom of psychiatric or neurological disorders. Aside from accounts of pseudobulbar palsy, the literature has generally ignored adult crying as a clinical event. Our study of medically or surgically hospitalized patients, most of whom were male, who cried enough to prompt psychiatric consultation found that CNS disorders were a common occurrence. We recommend a systematic diagnostic approach to patients who cry.

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Posttraumatic Stress Disorder Among Frontline Soldiers With Combat Stress Reaction: The 1982 Israeli Experience

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One year after the 1982 Lebanon War, the authors assessed the prevalence, type, and severity of posttraumatic stress disorder in a large representative sample of Israeli soldiers who had been treated for combat stress reactions. Comparisons were made with a group of soldiers who had fought in the same battles but had not been treated for this reaction. A dramatically higher percentage of soldiers with combat stress reaction (59%) than of soldiers without combat stress reaction (16%) developed posttraumatic stress disorder. Age was significantly associated with posttraumatic stress disorder. The authors discuss the differential quality of posttraumatic stress disorder among both groups as well as the factors facilitating recovery.

(Am J Psychiatry 1987; 144:448–454)

The intense stress of war has long been recognized as a pathogenic agent inducing or aggravating somatic and psychiatric disorders (1–3). Exposure to combat stress may result in an array of disturbances, the most common of which is combat stress reaction, also known as combat exhaustion or battle shock. This syndrome is marked by a sense of inadequacy in coping with a real and acute threat to life. The soldier experiences a feeling of loss of control accompanied by overwhelming anxiety and a marked decline in functioning (4). Combat stress reaction symptoms are not uniform but include labile and polymorphic manifestations: restlessness, psychomotor retardation, psychological withdrawal, signs of sympathetic activity, startle reactions, confusion, nausea and vomiting, and paranoid reactions (1, 4). Despite the extreme variability of this phenomenon, a common denominator can be identified: the soldier ceases to function and/or begins to function in an extreme manner that usually endangers himself and/or his comrades.

Despite agreement concerning the short-term debilitating effects of combat stress reaction, very few studies have actually assessed its long-term sequelae. Those which have attempted to do so (5, 6) have serious limitations. Kettner (5) compared a group of 35 United Nations (UN) soldiers serving in the Congo (Zaire) in 1961 who had been diagnosed by Swedish psychiatrists as suffering from combat stress reaction with a comparable group of UN soldiers not so diagnosed. He found that the two groups did not differ in long-term adjustment or mental health. Notwithstanding the precision of this innovative study, Kettner's sample was small and drawn from a highly selective population that differs from other populations of army recruits. Both of these facts make generalization difficult.

Our earlier study (6) was a preliminary investigation assessing the subsequent military adjustment of Israeli combat stress reaction casualties of the 1973 Yom Kippur War. That early work did not include all the combat stress reaction casualties of the Yom Kippur War, and, as we indicated, we did not know whether our sample was representative. The outcome measure used was the soldier's military profile, which is the Israel Defense Forces rating of a soldier's physical and mental health. Not only is this a specifically Israeli evaluation of combat fitness, but it has also been found to be an inadequate measure of mental status (7). The present study attempts to correct these deficiencies. Here we use a large representative sample of combat stress reaction casualties, a large matched control group, and more standardized and valid outcome measures. We also included cases of delayed combat stress reaction that occurred up to 1 year after the end of the Lebanon War.

In this study we hope to trace the long-term sequelae of combat stress reaction. The literature on general stress has suggested two hypotheses regarding long-term sequelae of stress: stress evaporation and residual stress (8). The stress evaporation hypothesis contends that after an initial brief, intense period of readjustment, there is usually a return to the premorbid level of

Received Oct. 3, 1985; revised March 28 and Aug. 19, 1986; accepted Sept. 17, 1986. From the Department of Mental Health, Israel Defense Forces Medical Corps. Address reprint requests to Dr. Solomon, Department of Mental Health, Medical Corps, Israel Defense Forces, Military P.O. Box 02149, Israel.

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functioning (9–11). In contrast, the residual stress hypothesis assumes that the mental health consequences of trauma are long-lasting, leaving the individual scarred and emotionally vulnerable for an extended period of time (8, 12, 13).

To determine which of these hypotheses may be most applicable to combat stress reaction, in this study we investigate one of several possible psychiatric sequelae of war, posttraumatic stress disorder. War is only one traumatic event that can give rise to posttraumatic stress disorder. It can result from a variety of traumatic experiences, such as rape, assault, road accidents, floods, confinement in a concentration camp, and a host of other man-made and natural disasters. Posttraumatic stress disorder can be assessed today by clear standardized criteria provided by *DSM-III,* published in 1980. Posttraumatic stress disorder is characterized by reexperiencing of the traumatic event, numbing of responsiveness to or reduced involvement with the external world, and a variety of autonomic, dysphoric, or cognitive symptoms.

This study assesses posttraumatic stress disorder in Israeli soldiers 1 year following their participation in the 1982 Lebanon War. The study has three specific aims: 1) to assess the prevalence and number of posttraumatic stress disorder symptoms among combat stress reaction casualties and matched control subjects, 2) to delineate a profile of posttraumatic stress disorder symptoms as defined in *DSM-III* criteria, and 3) to assess the effects of sociodemographic factors on posttraumatic stress disorder.

METHOD

Subjects

A sample of 716 male soldiers was drawn from two groups. The first, the combat stress reaction group, consisted originally of 470 frontline combat unit soldiers; 382 of these soldiers actually participated in this study, representing a response rate of 81%. Criteria for inclusion in this group were participation in frontline combat during the 1982 Lebanon War; referral for psychiatric intervention by the soldier's battalion surgeon during the war; diagnosis of combat stress reaction made on the battlefield by Israel Defense Forces clinicians, who are trained and experienced in the diagnosis of combat-related reactions; no indication of physical injury; and no indication in the clinicians' reports of other combat-related disorders, such as brief reactive psychosis or fictitious disorders. The research staff determined eligibility by using records of clinicians' diagnoses made on the battlefield. All 470 soldiers in the original sample were treated for combat stress reaction; 155 (33%) received frontline treatment and 315 (67%) were evacuated to rear treatment facilities. (A detailed account of the impact of frontline treatment on subsequent symptoms in these soldiers has been published [14].)

The second group was our control group. For each of the original 470 soldiers with combat stress reaction, a matched control subject was randomly selected from among eligible soldiers who had similar sociodemographic features. Specifically, the control subjects were matched with the group of soldiers with combat stress reaction for age, education, and military rank and assignment. They had participated in the same frontline combat units as the soldiers with combat stress reaction but had not shown symptoms of combat stress reaction. Of the 470 original control subjects, 334 actually participated in the study, representing a response rate of 71%.

Of course, the possibility that some of the soldiers in the control group may have suffered an unreported incident of combat stress reaction must be considered. However, since the symptoms of an episode of combat stress reaction are quite visible and readily identifiable in battle, where they endanger so many other people, there is good reason to believe that the number of unidentified cases of combat stress reaction in the control group was negligible.

The difference in number of subjects between combat stress reaction and control groups is due to the differential rate of participation in each group.

To confirm that the subjects who participated in the study were in fact representative of the target population, we checked their military records. These records indicated that the soldiers who participated in this study did not differ significantly from nonparticipants in their sociodemographic and military background, premilitary adjustment, or intelligence.

Table 1 presents the demographic characteristics of the combat stress reaction and control groups. Most of the subjects in both groups (507 of 716—71%) ranged in age from 18 to 33 years (median age=28.5 years); 128 (18%) had completed eighth grade (elementary school), 187 (26%) had had at least some high school, 241 (34%) had completed high school, and 132 (18%) had studied beyond high school. The majority—405 (57%)—were born in Israel, 148 (21%) were of African or Asian origin, and 104 (15%) were of European or American descent. Four hundred fifty-three (63%) were married. Three hundred twelve (44%) were of above-average and 150 (21%) of below-average economic status. Chi-square tests indicated that the study groups did not differ significantly from each other in any sociodemographic or military variable.

Measures

Posttraumatic stress disorder was assessed by using a self-report questionnaire based on *DSM-III* criteria. This inventory consists of 13 statements describing the *DSM-III* symptoms of posttraumatic stress disorder as adapted for war trauma. The respondent was asked to indicate whether he had experienced each of the symptoms within the past month. For items answered positively, the respondent was asked to indicate further whether onset had been before the 1982 war,

TABLE 1. Characteristics of Israeli Soldiers With and Without Combat Stress Reaction During 1982 Lebanon War

Characteristic	Soldiers With Combat Stress Reaction (N=382)		Soldiers Without Combat Stress Reaction (N=334)	
	N	%	N	%
Age (years)				
18–25	105	27	83	25
26–28	84	22	70	21
29–32	90	24	75	22
33 or more	90	24	93	28
Not known	13	3	13	4
Education				
Elementary (eighth grade)	75	20	53	16
Some high school	96	25	91	27
Completed high school	128	34	113	34
University	71	19	61	18
Not known	12	3	16	5
Country of birth				
Asia or Africa	73	19	75	22
Europe or America	58	15	46	14
Israel	227	59	178	53
Not known	24	6	35	10
Marital status				
Not married	114	30	92	28
Married	250	65	203	61
Not known	18	5	39	12
Economic status[a]				
High	53	14	48	14
Medium	106	28	105	31
Average	100	26	99	30
Low	93	24	57	17
Not known	30	8	25	7
Military rank				
Private or corporal	182	48	160	48
Up to sergeant major	171	45	151	45
Lieutenant or above	12	3	5	1
Not known	17	4	18	5

[a]Economic status was measured by asking the respondent to evaluate his income relative to the mean national income at the time of the study.

during or immediately after the war, or within the previous month. The answer "before the war" was intended to uncover residual symptoms of posttraumatic stress disorder in soldiers who had participated in previous wars. Since less than 2% of the soldiers reported having posttraumatic stress disorder symptoms before the 1982 war, this answer was excluded from further analyses.

The 13 inventory statements were divided into three categories of symptoms corresponding to the three *DSM-III* criteria for the diagnosis of posttraumatic stress disorder.

The first category was reexperiencing of the trauma (three items), as evidenced by 1) recurrent and intensive recollections of the traumatic event, 2) recurrent dreams of the event, and/or 3) sudden acting or feeling as if the event were recurring (feeling of being in combat).

The second category was numbing of responsiveness to or reduced involvement with the external world (three items), as evidenced by 4) markedly diminished interest in significant activities (lack of interest in work and family), 5) feeling of detachment or estrangement from others, and/or 6) constricted affect (lack of anger in situations that used to provoke anger).

The third category was additional symptoms (seven items): hyperalertness, sleep disturbance, survivor guilt or guilt feelings about behavior during the war, memory impairment or concentration difficulties, avoidance of activities that trigger recall of the event, and/or intensification of symptoms with exposure to events that symbolize the trauma. For the inventory these seven items were translated into 7) hypersensitivity to noise, 8) general insomnia, 9) memory difficulties, 10) survivor guilt feelings, 11) avoidance of events that recall combat, 12) sleep difficulties, and 13) guilt feelings about conduct.

To be diagnosed as suffering from posttraumatic stress disorder, a person must have experienced a previous traumatic event. All soldiers in both the combat stress reaction group and the control group met this criterion. In this study, a soldier was considered to suffer from posttraumatic stress disorder if he reported at least one of the symptoms in each of categories one and two and at least two symptoms in category three. Posttraumatic stress disorder was considered chronic if symptoms lasted for more than 6 months and delayed if onset occurred 6 months after the trauma.

To test its reliability, the posttraumatic stress disorder inventory was administered twice within a 1-week interval to a small group of 20 soldiers. The percentage of agreement was 82%, indicating high test-retest reliability.

To test its concurrent validity, posttraumatic stress disorder inventory results for the entire sample were correlated with scores on the Impact of Event Scale (15), a measure designed specifically to assess the impact of traumatic experiences. The posttraumatic stress disorder inventory results correlated with the Impact of Event Scale scores both in intrusion ($r=.62$, $N=659$, $p<.01$) and avoidance ($r=.40$, $N=659$, $p<.01$), thus supporting concurrent validity for the posttraumatic stress disorder measure. Given the lack of other concurrent diagnoses, however, these correlations do not support the specificity of our diagnostic criteria for posttraumatic stress disorder.

The clinical validity of the 13-item inventory was assessed by concurrent clinical interviews of a subsample of 114 soldiers randomly selected from among the subjects who completed the inventory. Clinicians who had experience with posttraumatic stress disorder assessed the presence of each symptom on the posttraumatic stress disorder inventory and also determined whether the soldiers suffered from the syndrome. Concordance percentages were calculated for each symptom as well as for the final diagnosis. Concordance percentages for the 13 symptoms ranged from 69% to 80%; the rate was 75% for the final diagnosis. This reflects a high level of agreement between the self-report inventory and the clinical diagnosis of posttraumatic stress disorder.

Procedure

Approximately 1 year following their participation in the 1982 Lebanon War, subjects were asked to report to the headquarters of the Surgeon General of the Israel Defense Forces. The request was accompanied by a personal letter explaining that they had been selected at random to participate in a routine periodical health assessment conducted as part of the Medical Corps's concern for the well-being of its regular and reserve soldiers. Subjects were seated in groups of seven to 19 soldiers each while they individually filled out a battery of questionnaires. Soldiers were informed that their participation was voluntary and were assured that the data would remain confidential, in no way affecting their status in military or civilian life.

Although secondary gain considerations may have led subjects to overly endorse symptoms, this possibility was partially negated by the great overlap between subjects' responses and the evaluation of experienced clinicians. In addition, combat stress reaction and control subjects completed the inventory simultaneously and were clearly informed that their military health profile ratings would not be changed on the basis of their reports. Soldiers were aware that a different administrative unit was responsible for claims for physical or mental injuries. In fact, only a negligible number of subjects actually requested a change in their military health profile rating.

RESULTS

Of the 382 soldiers who had experienced combat stress reaction, 225 (59%) had posttraumatic stress disorder 1 year after the Lebanon War; 53 (16%) of the 334 soldiers who had not experienced combat stress reaction had posttraumatic stress disorder 1 year after the war. The difference between groups was significant (χ^2=38.28, df=l, p<.0l). Although differences between combat stress reaction and control groups were expected, the percentage suffering from posttraumatic stress disorder in both groups was surprisingly high.

In each group, most of the cases of posttraumatic stress disorder were chronic: 189 (84%) of the soldiers in the combat stress reaction group and 32 (60%) of the soldiers in the control group reported the onset of symptoms to have been during or immediately after the war. However, 20 (38%) of the 53 soldiers in the control group who developed posttraumatic stress disorder reported delayed symptoms (6 months after combat) of the disorder, compared with 34 (15%) of the 225 soldiers with combat stress reaction who developed posttraumatic stress disorder (χ^2=14.61, df=1, p<.01).

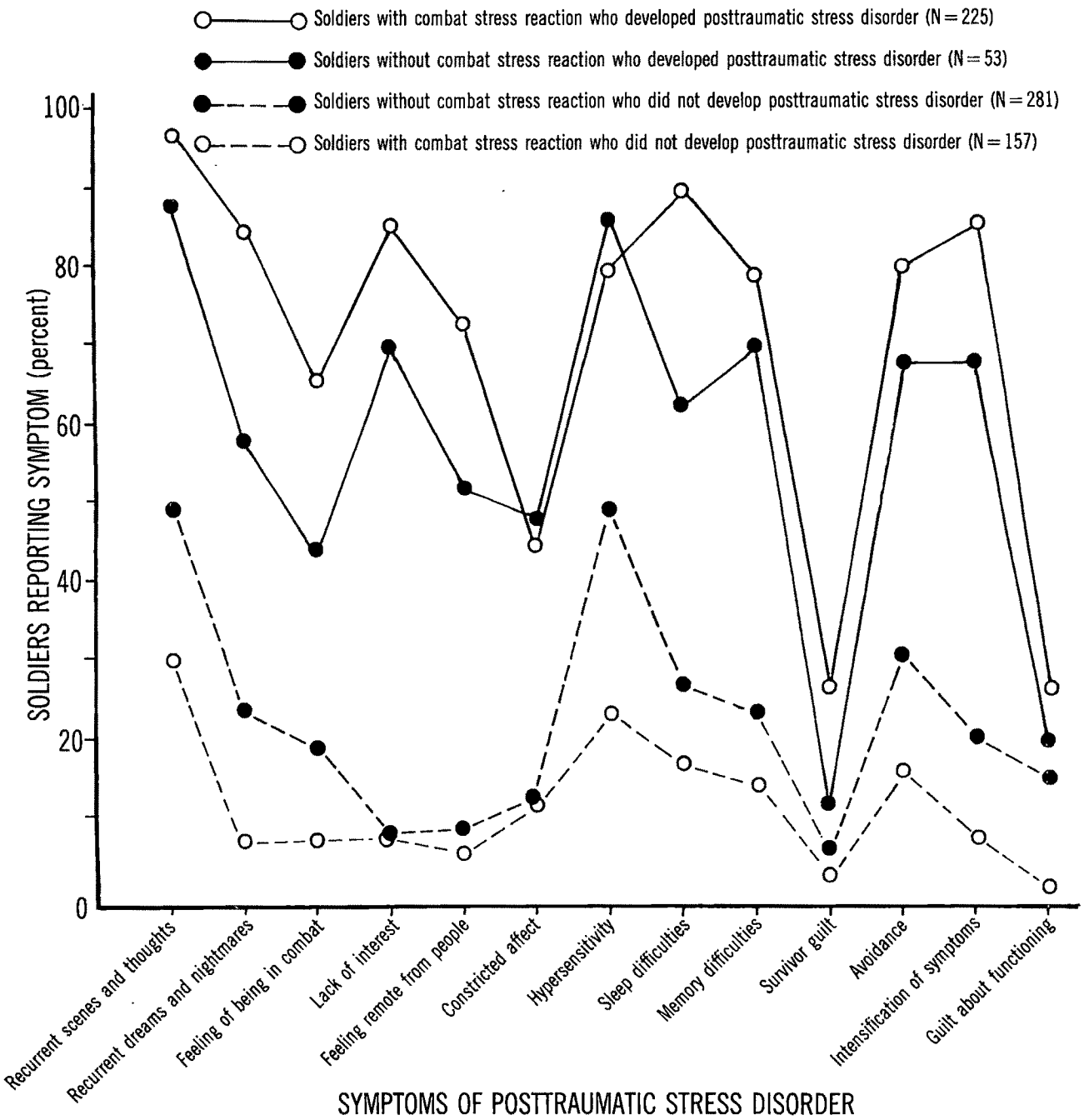
DSM-III criteria are customarily used dichotomously to determine the presence or absence of posttraumatic stress disorder. The present study, however, went beyond the dichotomous diagnosis and took into consideration the number of symptoms each soldier noted was present. The number of symptoms was analyzed by a two-way analysis of variance (ANOVA) (Study Group by Presence of Posttraumatic Stress Disorder). Significant main effects of group (F=64.34, df=1, 674, p<.01) were obtained. Group differences stemmed from the larger mean number of symptoms reported present by soldiers in the combat stress reaction group (mean=6.04) than in the control group (mean=4.50). Another main effect was due to the higher mean number of symptoms reported present by soldiers who developed posttraumatic stress disorder (mean=7.70) than by soldiers who did not develop posttraumatic stress disorder (mean=1.84). The lack of interaction, however, suggests that subjects who suffered from combat stress reaction during the war still reported more symptoms as a group than did the control group, regardless of current posttraumatic stress disorder status.

The preceding analyses focused on the global aspects of posttraumatic stress disorder. Here we examine the contribution of the individual symptoms to the syndrome. Figure 1 presents the symptoms reported as present by four groups of subjects: soldiers who had experienced combat stress reaction during the war who did or did not develop posttraumatic stress disorder and soldiers who had not experienced combat stress reaction during the war who did or did not develop posttraumatic stress disorder. Three patterns clearly emerge. First, all four curves are almost parallel. Neither the presence or absence of posttraumatic stress disorder nor group affiliation led to a differently shaped curve. Whether symptoms were reported by many of the soldiers in each group or not, they were reported proportionately by all four groups. Second, the curves show that not all symptoms were reported as often as others—some were more prevalent. Some symptoms, such as recurrent recollections of the war, were reported by almost all posttraumatic stress disorder casualties, while others, such as survivor guilt and lack of anger, were reported by very few. Third, more subjects with posttraumatic stress disorder, regardless of whether they had had combat stress reaction, reported more of each of the 13 *DSM-III* symptoms than did subjects in the other groups.

We also examined the contribution of sociodemographic variables to posttraumatic stress disorder status in the combat stress reaction and control groups. The relation between each variable and posttraumatic stress disorder was assessed by chi-square tests separately for each group. The following variables were assessed for each subject: age, country of birth, level of education, marital status, and current economic status.

A significant relationship between age and posttraumatic stress disorder was found in the combat stress reaction group: 67 (74%) of the soldiers who had had combat stress reaction and who were 33 years old or older had posttraumatic stress disorder, compared with 52 (50%) of combat stress reaction subjects

FIGURE 1. Posttraumatic Stress Disorder Symptoms in Israeli Soldiers With and Without Combat Stress Reaction During 1982 Lebanon War Who Did or Did Not Develop Posttraumatic Stress Disorder 1 Year Later



18–25 years old, 51 (61%) of those 26–28 years old, and 47 (52%) of those 29–32 years old (χ^2=9.02, df=3, p<.01). No significant relationship between posttraumatic stress disorder and age was found in the control group. This means that older subjects tended to suffer more from the sequelae of combat stress reaction but that age was not a risk factor for posttraumatic stress disorder among soldiers who had not had combat stress reaction.

Similarly, a significant relationship between marital status and posttraumatic stress disorder was found in the combat stress reaction group (χ^2=4.34, df=1, p<.05). Since, however, there was a significant relationship between the marital status and age of all of the subjects (χ^2=168.67, df=3, p<.01), we analyzed the rate of posttraumatic stress disorder with age kept as a covariate. No significant effect was found, implying that the difference in rate of posttraumatic stress disorder between married and unmarried soldiers reflected only differences in age.

DISCUSSION

The rate of posttraumatic stress disorder among combat stress reaction casualties (59%) was overwhelmingly higher than that among control subjects (16%). These figures must be interpreted cautiously, however. Although 59% seems to be a high rate indeed, there is little in the literature to serve as a normative basis for comparison. Studies of Vietnam veterans (16, 17) found rates ranging from 24% to 48%; however, these studies did not directly address the connection between combat stress reaction and posttraumatic stress disorder.

As for the 16% rate of posttraumatic stress disorder among control group soldiers, it must be emphasized that this group was chosen on the basis of its similarity to the combat stress reaction group; it was not chosen as a representative sample of soldiers who participated in battle. Nonetheless, this rate also seems to be high in view of the fact that none of the soldiers with posttraumatic stress disorder in the control group had sought treatment.

The relatively high rates of posttraumatic stress disorder in both groups could be attributed to the prominence of war in Israeli society. The soldiers who had been traumatized in Lebanon, whether they had immediate or latent manifestations, continued to be bombarded by threatening military stimuli, which may well have impeded their recovery. The Lebanon War, Israel's longest war, had not completely ended when this study was undertaken. Although the heavy fighting lasted only through several weeks of the summer of 1982, the cease-fire signed in August of that year did not put an end to all hostilities. Israeli soldiers remained in Lebanon, where periodic flareups continued to occur. All of our subjects, like other Israeli men between the ages of 22 and 45, were still part of Israel's reserve forces and could be recalled at any point for active duty in Lebanon.

The differences in posttraumatic stress disorder observed in the combat stress reaction and control groups were not only quantitative but also qualitative. The groups differed qualitatively in the number and duration of reported symptoms of posttraumatic stress disorder. The subjects in the combat stress reaction group who developed posttraumatic stress disorder reported a much higher number of symptoms than did subjects in the control group who developed posttraumatic stress disorder. This difference, which is overlooked in the accepted *DSM-III* criteria for the diagnosis of posttraumatic stress disorder, suggests that the posttraumatic stress disorder in the combat stress reaction group was more intense in nature than it was in the control subjects who developed posttraumatic stress disorder without antecedent combat stress reaction. As for the duration of symptoms, most of the cases of posttraumatic stress disorder in both groups were chronic: that is, the onset of symptoms was reported to have been during combat or shortly thereafter. Nonetheless, the control group reported twice the rate of delayed posttraumatic stress disorder (symptoms beginning at least 6 months after combat) than did the combat stress reaction group.

Guilt feelings and constricted affect (lack of anger in situations that had aroused anger), listed by *DSM-III* as symptoms of posttraumatic stress disorder, did not play the prominent role that they reportedly have played in other forms of trauma (18, 19) or in other clinical reports of war experiences (20, 21). There are several possible explanations for these findings. First, it is possible that guilt and constricted affect are not necessary components of psychopathology following combat reactions. Second, the present findings may be attributed to the unique characteristics of the 1982 Lebanon War: the absence of atrocities and the positive attitude of the Israeli population toward returning soldiers. Israeli soldiers went to great lengths to protect civilian populations and were not involved in any atrocities. At the same time, although the Lebanon War was not supported by large segments of the Israeli population, the soldiers who fought it were. We cannot definitively determine on the basis of our data which of the above was more relevant to our findings.

The finding that none of the soldiers with posttraumatic stress disorder in the control group had sought treatment is consistent with earlier findings regarding Vietnam veterans. Figley and Sprenkle (22) found that a high percentage of Vietnam veterans with delayed stress problems avoided seeking any sort of treatment. Similarly, the major epidemiological study of Vietnam veterans (17) indicated that the overwhelming majority of these veterans with identified difficulties were reluctant to seek psychiatric treatment. Nonetheless, in the current Israeli context the disinclination to seek treatment is somewhat surprising. Had these soldiers sought help for their war-related disturbances within the framework of the Israel Defense Forces and thus identified themselves as posttraumatic stress disorder casualties, they would have averted the very real risk of being sent back to the front.

We offer three possible explanations for untreated posttraumatic stress disorder in our control group. One is that the severity of posttraumatic stress disorder in the control group was less than it was in the combat stress reaction group. Soldiers in the control group who developed posttraumatic stress disorder may not have been aware that they had a treatable disorder. Earlier studies (23) have shown that seeking treatment for psychiatric disturbances and adopting the sick role are related to the severity of symptoms. A second possibility is that even if the control subjects who developed posttraumatic stress disorder were aware of their distressing symptoms, they perceived them as an appropriate response to the stresses of war. A third explanation is that soldiers who did not identify themselves as posttraumatic stress disorder casualties had a high motivation to continue serving in the army and were not interested in obtaining the possible secondary gains of illness. In Israel, masculine identity is very

strongly associated with army service. Identifying himself as ill may well have cost a soldier a heavy price in both self-esteem and social acceptance.

Little is known about the long-term sequelae of combat stress reaction. The present study, which investigated subsequent diagnosed posttraumatic stress disorder in a large group of combat stress reaction casualties and comparable control subjects, can serve as a first step in increasing our knowledge of this complex phenomenon. To be sure, posttraumatic stress disorder is not the only possible psychiatric outcome of combat stress reaction. Other psychiatric disorders, such as depression, adjustment disorders, and alcoholism, may also ensue. More research assessing the spectrum of combat-related psychiatric disorders and using multicohort longitudinal designs is needed to attain a better understanding of the long-term sequelae of combat stress reaction.

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TRH-Induced TSH Response in Healthy Volunteers: Relationship to Psychiatric History

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The authors measured thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone in 32 healthy volunteers who had never sought or received psychiatric treatment. Nine (28%) had a family or personal history of depression or alcoholism. Five of these nine subjects and one of 22 subjects without such a history showed TSH blunting (TSH data were not available for one subject). This difference was statistically highly significant. Although there were sex differences in TSH response, TSH blunting occurred most frequently in men with a family or personal history of depression or alcoholism. The fault may have utility as a marker of past episodes or as a true marker of trait.

(Am J Psychiatry 1987; 144:455–459)

There is now overwhelming evidence that thyroid-stimulating hormone (TSH) response to thyrotropin-releasing hormone (TRH) is blunted in some patients with major depression. Several aspects of TSH blunting in depression such as sensitivity, specificity, underlying mechanisms, pathophysiologic significance, and possible clinical utility have been reviewed in detail (1–3).

It is less well understood whether TSH blunting is state rather than trait related. The fault has been observed mainly in depressed and alcoholic patients, suggesting that it is not disease specific. In both conditions, TSH blunting occurred during the acute state of the disease and (with reduced frequency) after its symptomatic remission. For example, the frequency of TSH blunting in acutely sick and remitted depressed patients was 26% and 14%, respectively (3). The corresponding rates for alcoholic patients during acute withdrawal and after prolonged sobriety were 50% and 31% (3–5). Thus, in both depression and alcoholism, TSH blunting appears to be sometimes a state marker and sometimes a trait marker. As a state marker, it can occur in the acute states of both diseases without persisting into remission, which suggests that it may play a role in their pathophysiology (1–6). As a marker of past episodes or a true marker of trait, TSH blunting can occur in the remitted states of both diseases, which suggests that it may be helpful in identifying subjects with either a past history of or a high vulnerability for these conditions. The present report was stimulated by the latter considerations. TSH response was evaluated to determine its possible trait marker utility in normal, healthy volunteers.

METHOD

We studied 32 consecutively admitted normal subjects 19 to 42 years of age (mean±SD=25.6±6.5 years). They were recruited by an advertisement in the Duke University newspaper; the majority were medical students. After a telephone contact, subjects were given an appointment for the initial study workup, consisting of a laboratory screen (SMA-15, thyroid panel, urinary status, and EKG), a pregnancy test for female subjects, a thorough physical examination, and assessment of psychiatric history.

None of the subjects presented historical, chemical, or physical evidence of any endocrine disorder or other major somatic illness. None had taken medications or abused alcohol or drugs for at least 12 months before testing. No female subject was pregnant or taking oral contraceptives. All were euthyroid at the time of testing and had given written informed consent.

During the first appointment, all subjects were given a formal psychiatric interview by two independent psychiatrists (R.M., P.T.L.). During the interview, subjects were diagnosed according to *DSM-III* criteria and Research Diagnostic Criteria (RDC). Family history data were also collected with the family history RDC, and a pedigree was drawn. This was based on the interview with the subject; family members were not interviewed. Final diagnoses regarding a personal or family history were made by consensus during a conference and were based on RDC and family history

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Supported in part by NIMH grant MH-39237.

The authors thank Ms. Winona W. Gee for assistance in preparing the manuscript and Mr. Gordon Daughtry for statistical analysis of the data.

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RDC data. Assessment of potential depressive symptoms was based on clinical judgment and scores on conventional rating scales for depression. Both subjects with and subjects without a family or personal history were included. No subject, including those with a personal history, had ever sought or received psychiatric treatment or counseling. Moreover, no subject fulfilled the RDC for a present episode or was actually depressed at the time of testing. Scores on both objective depression scales (Hamilton Rating Scale for Depression [7] and Montgomery-Asberg Scale [8]) and subjective scales (Carroll Rating Scale for Depression [9] and 100-mm-line test for depression [10]) were normal. All subjects had a Hamilton score (items 1–17) of less than 8 at the time of testing.

After the initial study workup, subjects were given a second appointment for injection of TRH. This was performed by a physician (K.T.) who was blind to the results of the psychiatric evaluation. All subjects received an injection of 0.5 mg of TRH in a standard fashion (1–3). Serum samples were frozen at −20°C until they were assayed in duplicate. FT_4 index and total T_4 were assayed as described previously in detail (4–6). TSH was assayed with a monoclonal antibody assay that is commercially available (Serono Laboratories). Intra-assay coefficient of variance for the TSH assay was less than 5%, and its lower limit of sensitivity was 0.5 μU/ml. TSH blunting was defined as a Δmax TSH (maximum rise over baseline) of less than 5.9 μU/ml. This definition was based on the analysis of the TSH distribution curve in a different group of 73 normal subjects. None of these subjects had a personal or family history of any psychiatric disorder. TSH responses were unimodally distributed, with a mean± SD Δmax TSH of 11.7±5.8 μU/ml. A subnormal TSH response was then defined as mean Δmax TSH minus 1 SD. Two other definitions, more frequently used in the literature, were also used for comparison.

Differences between groups in hormonal values were analyzed by use of Student's t test and two-way analysis of variance (ANOVA) (11). The difference in frequency of TSH blunting between groups was analyzed by use of Fisher's exact test (11). To assess the possible marker utility of TSH blunting, the fault was evaluated as to its sensitivity (i.e., the frequency of true positive results obtained when the test is applied to subjects known to have the disease), specificity (i.e., the frequency of true negative results when the test is applied to subjects known to be free of the disease), and predictive value (i.e., the percentage of true positive results when the test is applied to a population containing both healthy and diseased subjects) (12).

RESULTS

Psychiatric History and TSH Response

Nine (28%) of 32 subjects had a family or personal history, or both, of depression or alcoholism. All family histories concerned alcoholic fathers, and all personal histories concerned either alcoholism or minor depression. Five subjects had a personal history, two subjects a family history, and two subjects both personal and family histories (table 1). Five of 22 female and four of 10 male subjects had a history; this distribution was not statistically significant. However, subjects with a history had a significantly higher Hamilton score (items 1–17) than did subjects without a history (mean±SD=4.0±3.6 versus 0.9±1.5; $p<.005$, Mann-Whitney test). This difference was due to higher ratings on four items: psychic anxiety (six of nine subjects), somatic anxiety (three subjects), hypochondriasis (two subjects), and sleep disturbances (one subject).

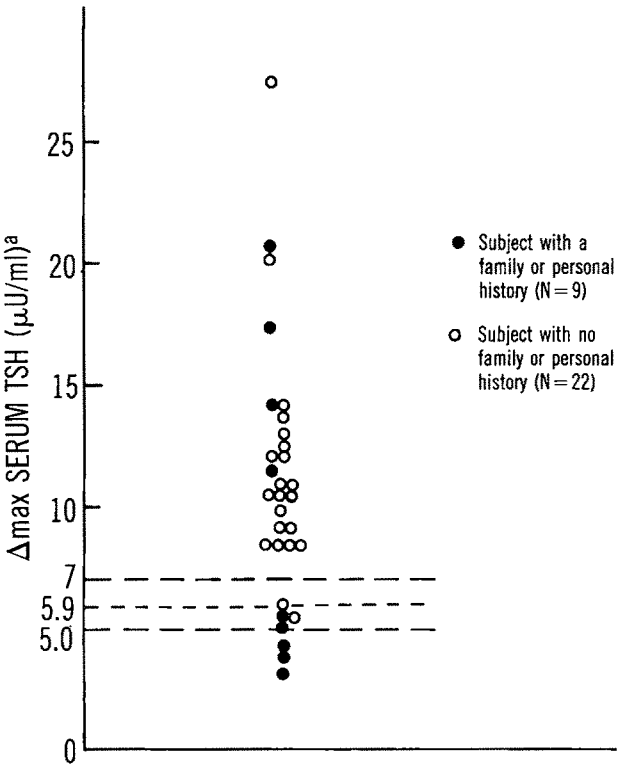
TABLE 1. Relationship Between Family or Personal History of Depression or Alcoholism and TSH Response to TRH in Nine Normal Subjects

Subject	Age (years)	Sex	History and Rating[a]		Δmax TSH (μU/ml)
			Family	Personal	
1	19	F	0	Minor depression; 2	5.7
2	24	M	Father alcoholic; 1	0	4.4
3	26	M	0	Alcoholism; 2	5.2
4	39	F	0	Minor depression; 2	20.7
5	30	F	Father alcoholic; 1	0	14.1
6	20	F	0	Minor depression; 2	17.4
7	25	F	Father alcoholic; 2	Minor depression; 2	11.6
8	41	M	Father and two brothers alcoholic; 1	Alcoholism, abstinent 3 years; 1	3.1
9	41	M	0	Minor depression; 1	4.0

[a]0=no history, 1=definite history, 2=likely history.

Five (55%) of the nine subjects with a history showed TSH blunting, defined as a max TSH of less than 5.9 μU/ml (table 1). In contrast, only one (5%) of the 22 subjects with no history showed TSH blunting (no TSH data were available for one subject). This difference was statistically highly significant ($p=.004$, Fisher's exact test). Figure 1 details the marker utility of TSH blunting in confirming the history data. As shown, sensitivity and specificity were inversely related (the higher the former, the lower the latter). For example, when TSH blunting was defined as a Δmax TSH of less than 5.0 μU/ml, sensitivity was 33%, specificity 100%, and predictive value 100%. In contrast, when a Δmax TSH of less than 5.9 μU/ml was used, sensitivity was 55%, specificity 95%, and predictive value 83%. A definition of the fault as a Δmax TSH of less than 7.0 μU/ml appeared to have no further advantage, since sensitivity remained the same and specificity and predictive value decreased (figure 1).

FIGURE 1. TSH Response to TRH in Normal Subjects With and Without a Family or Personal History of Depression or Alcoholism



[a]The sensitivity, specificity, and predictive value for three TSH blunting criteria are as follows—Δmax TSH<5.0 μU/ml: 33%, 100%, 100%, respectively; Δmax TSH<5.9 μU/ml: 55%, 95%, 83%; Δmax TSH<7.0 μU/ml: 55%, 91%, 71%.

TABLE 2. Hormonal Values in Normal Men and Women

Item	Men (N=10) Mean	Men (N=10) SD	Women (N=22)[a] Mean	Women (N=22)[a] SD	Significance[b] t (df=29)	Significance[b] p
Age (years)	28.4	7.1	24.3	6.0	—	n.s.
TSH (μU/ml)						
Baseline	1.1	0.6	1.7	0.8	2.08	.05
Peak	7.8	2.8	14.5	5.5	4.58	.001
Δmax	6.7	2.6	12.8	5.0	4.61	.001
T_4 (μg/dl)	7.7	1.1	8.8	2.0	—	n.s.
FT_4 index	2.3	0.4	2.4	0.4	—	n.s.
T_3 uptake (%)	30.0	3.0	27.4	3.4	2.08	.05

[a]N=21 for TSH data.
[b]Student's t test for unmatched samples.

Sex Distribution of Hormonal Values

The 10 men and 22 women were comparable in mean age and in serum levels of FT_4 index and total T_4. However, TSH levels, both at baseline and after TRH stimulation, were significantly lower and T_3-uptake values were significantly higher in men (table 2). Furthermore, five (50%) of the 10 men showed TSH blunting, compared to one (5%) of the 21 women (p=.006, Fisher's exact test). These sex differences necessitated that all data regarding the relationship between TSH response and a personal or family history of depression or alcoholism be further analyzed separately for each sex.

Two-way ANOVA with sex and psychiatric history as factors revealed a significant sex effect for TSH (baseline, peak, and Δmax) and T_3 uptake. Moreover, there was a significant history effect for T_4 and T_3 uptake. However, for no variable was there a significant Sex × History interaction (table 3). In regard to TSH response, it is worth noting that all four of the men with a history showed TSH blunting, compared to one of six (17%) without a history (p=.024, Fisher's exact test). No such relationship was observed among the women, of whom one of five with a history and none of 16 without a history had shown TSH blunting.

Five male subjects showed TSH blunting, and the remaining five had a normal TSH response (table 4). T_3-uptake values were significantly lower in subjects with TSH blunting. There was also a tendency for subjects with TSH blunting to be older, and to have lower FT_4-index values. Baseline TSH and T_4 levels were similar in both groups.

CONCLUSIONS

Nine (28%) of 32 normal volunteers studied in this report had a family or personal history of depression or alcoholism. All family histories concerned alcoholic fathers, whereas personal histories involved either minor depression or alcoholism. Both family and personal history data thus concerned disorders in which the TSH response has been consistently reported to be blunted, i.e., depression (see references 1–3 for a review) and alcoholism (4, 5, 13–17). However, none of the subjects with a personal history had ever sought or received any psychiatric treatment or counseling; further, they did not fulfill criteria for a present episode and were not depressed at the time of testing. Nevertheless, the mean Hamilton depression score was significantly higher in subjects with a history than in those without a history. This difference was mainly due to mild anxiety and sleep disturbances.

Five (55%) of nine subjects with a history and one (5%) of 22 subjects without a history showed TSH blunting, defined as a Δmax TSH of less than 5.9 μU/ml. The difference between groups was statistically highly significant, suggesting that TSH response may be of some utility in confirming the psychiatric history data. These data are consistent with one report in the literature. Robertson and coworkers (18) studied 17 normal control subjects with the TRH test. Six (35%) of the subjects were found to have a personal history of depression or alcoholism or a family history of depression. Five (83%) of the six showed TSH blunting (defined as a Δmax TSH of less than 5.0 μU/ml), but none of the other 12 did. However, it is unclear which factors might have contributed to the difference in

TABLE 3. Hormonal Values in Normal Men and Women With and Without a Family or Personal History of Depression or Alcoholism

	Men				Women						
	History (N=4)		No History (N=6)		History (N=5)		No History (N=17)[a]		Two-Way ANOVA (Sex × History)		
Item	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F	df	p
Age (years)	33.0	9.3	25.3	3.4	26.6	8.2	23.5	5.4	—	—	n.s.
TSH (μU/ml)											
Baseline	0.9	0.5	1.3	0.7	2.0	0.7	1.6	0.8	5.15[b]	1,27	.05
Peak	5.1	1.4	9.6	1.8	15.9	6.2	14.2	5.5	12.73[b]	1,27	.001
Δmax	4.2	0.9	8.3	1.8	13.9	5.7	12.6	5.0	12.57[b]	1,27	.001
T_4 (μg/dl)	7.6	1.0	7.7	1.2	10.3	1.3	8.0	1.5	5.86[c]	1,28	.05
FT_4 index	2.2	0.2	2.4	0.5	2.6	0.3	2.3	0.3	—	—	n.s.
T_3 uptake (%)	28.5	2.1	31.1	3.2	25.4	3.4	28.3	3.2	5.62[b]	1,27	.05
									4.90[c]	1,27	.05

[a]N=16 for TSH data.
[b]Significant main effect for sex.
[c]Significant main effect for history.

TABLE 4. Hormonal Values in Normal Men With and Without TSH Blunting

	TSH Blunting (N=5)[a]		TSH Response (N=5)		Significance[b]	
Item	Mean	SD	Mean	SD	t(df=8)	p
Age (years)	32.4	8.1	24.4	2.9	2.07	.072
TSH Baseline (μU/ml)	1.0	0.5	1.2	0.7	—	n.s.
T_4 (μg/dl)	7.4	1.0	8.0	1.2	—	n.s.
FT_4 index	2.1	0.3	2.6	0.4	2.22	.057
T_3 uptake (%)	27.8	2.3	32.2	1.5	3.56	.01

[a]Δmax TSH<5.9 μU/ml.
[b]Student's t test for unmatched samples.

sensitivity between Robertson and associates' and our data. Obviously, the marker utility of the TSH response depends largely on the definition of the fault. For example, when the more traditional definition (Δmax TSH of less than 5.0 μU/ml) was used, the fault had a sensitivity of 33%, a specificity of 100%, and a predictive value of 100%. Thus, sensitivity was low and specificity and predictive value were perfect. It is worth noting that all subjects with a Δmax TSH of less than 5.0 μU/ml also had a definite family or personal history as judged by the RDC. Moreover, when this traditional definition of the fault was used, the frequency of TSH blunting in normal subjects with a history was similar to that previously reported for acutely depressed (1, 2) and abstinent alcoholic (3–5, 17) patients (i.e., approximately 30%). In contrast, when blunting was defined as a Δmax TSH of less than 5.9 μU/ml, sensitivity was 55%, specificity 95%, and predictive value 83%. Thus, sensitivity was improved and specificity and predictive value decreased. An even more liberal definition of TSH blunting did not appear to be of further advantage.

There were large differences in the mean TSH response between male and female subjects. This finding, confirming other reports in the literature (see reference 19 for a review), necessitated the separate evaluation of hormonal responses for each sex. It also suggested that sex differences may have confounded results, since 50% of the men and only 5% of the women showed TSH blunting. Analysis of TSH response data in all subjects by using two-way ANOVA, with sex and history as factors, revealed significant sex-related differences but no history effects or Sex × History interaction. However, when the frequency of TSH blunting was analyzed separately for each sex, all men with a history showed TSH blunting, compared to 17% of the men without a history. In contrast, no such relationship was found among the women. Thus, TSH blunting was most consistently observed in the men with a history. Both etiology and pathophysiology of these TSH response differences in subjects with and without a history are not well understood. However, the data clearly suggest that male subjects may be more appropriate than female subjects to study possible associations between TSH blunting and a family or personal history of depression or alcoholism.

There are two methodologic shortcomings that necessitate a cautious interpretation of our data. First, assessment of family histories did not include interviews of family members. The frequency of such histories may thus have been over- or underestimated. Second, the data did not allow separate consideration of a personal and family history. It therefore remains unclear whether TSH blunting is a marker of a past episode or a true marker of trait. Nevertheless, the data do reveal a strong association between a personal or family history and TSH blunting and thus suggest that further studies in this field are warranted. Longitudinal assessments of depressed and alcoholic patients, studies of first-degree family members of such patients, and evaluations of subjects known to be at risk for developing alcoholism or depression are most likely to clarify whether TSH blunting is a marker of a past episode or a true marker of trait.

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Effects of Large Group Awareness Training on Participants' Psychiatric Status

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The impact of large group awareness training on psychiatric status was evaluated in two cohorts of participants. Clinical and Diagnostic Interview Schedule interviews were used to specify impact; a small number of stress reactions and no psychiatric casualties were identified in the more than 300 subjects studied.

(Am J Psychiatry 1987; 144:460–464)

The development of sensitivity training in the late 1940s stimulated psychiatry's interest in the emotional risk such activities posed for participants (1, 2). The rapid expansion of encounter groups in the early 1960s quickened the pace of published reports on psychiatric risk (3, 4). Beginning in the late 1970s the primary setting changed to large group awareness training. Organizations like *est* and Lifespring are two well-known examples of the for-profit expression of this motif in our society.

The basic Lifespring course involves about 300 participants, a trainer, and a dozen or so volunteer staff. Finkelstein et al. (5) provide a detailed description of *est*. Lifespring and *est* share many similarities, although their philosophy and proscriptive cognitive structures are distinct. Both use structured settings with sharp and specific ground rules of appropriate behavior and demeanor, a philsosophy that is distinct and articulate in order to provide a new cognitive framework, and a series of emotionally toned experiences that involve role playing, guided group interaction, and dyadic and small group exercises. Unlike Lifespring, *est* is a charismatic movement. Large group awareness training also provides an alternative peer network that extends beyond the training. Unlike sensitivity training and encounter groups, large group awareness training is less open to leader differences, since there is a detailed written plan which is followed with little variation from one training series to another.

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Supported in part by NIMH Research Scientist Award MH-20342 and funds from Lifespring, Inc.

The author thanks Irvin Yalom, M.D., who collaborated in the initial study of psychiatric risk, and Sandy Grayson, Ph.D., for assistance on the second and third studies.

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BACKGROUND: THE STUDY OF PSYCHIATRIC CASUALTIES

Each new form of experiential education (e.g., sensitivity training, encounter groups, large group awareness training) starts anew in limiting the cumulative development of information and generalization (6, 7, 8, 9, 10, 11). The generic label "experientially based education" only serves to bound an area; it does not provide conceptual power for comparison.

The early risk studies were case reports; these served to alert the field to the potential but cannot be responsive, in a scientific framework, to evaluating the toxic effects of such settings. Psychiatry's interest in the effects of experiential education appears to be straightforward; practitioners have encountered patients who were distraught and at times seriously psychiatrically ill subsequent to their participation. Beyond such a clinical goad, however, lies a more fundamental conceptual interest. Many perceive the processes utilized in large group awareness training as similar to those found in psychotherapy; questioning the use of such "powerful processes" by "untrained" people or in settings where even the most astute clinician would find it difficult to practice responsibly is appropriate. Findings that those who join such groups include a large proportion of troubled individuals add to the concerns. Many individuals who migrate to "human potential" settings are the same people, with identical motivations, who enter psychotherapy. Lieberman and Gardner (12) found that 81% of their growth center sample were currently or had recently been in psychotherapy. From a public health perspective, the combination of large numbers of participants and possible toxic effects merits investigation. The possibility of indirect negative effects through the diversion of a substantial number of people in most need from traditional psychiatric services is an important concern.

Accurate estimates on numbers of participants are difficult. In 1973, Lieberman et al. (10) estimated that

five million individuals had attended encounter groups. A recent analysis by Lieberman and MaCall (13) of the Mellinger and Balter National Survey (14) found a 2.6% prevalence rate for 1 year (1979) in their probability sample of more than 3,000 respondents between the ages of 18 and 79. This rate was based on participation in some form of group activity directed toward growth. Activities ranged from large group awareness training to local "Y" self-development groups. Finkelstein et al. (5) estimated in 1982 that 450,000 had participated in *est*. Inaccuracies may occur because of multiple participation patterns. Lieberman and Gardner (12) reported three to four "growth" activities per year.

Whatever the true rates, the Mellinger and Balter data strongly indicate (since it was a 1-year-point prevalence rate) that several million individuals are involved in a variety of human potential movement activities. Of these, a significant proportion participate in large group awareness training.

ESTIMATION OF NEGATIVE EFFECTS

A variety of approaches have been used to define negative effects. A diagnosable psychiatric condition that would not have existed had the person not participated in such activities is the ideal criterion, which is rarely reached. Some studies report on psychiatric trouble sufficient to bring someone under the care of a psychiatrist; others use psychiatric suffering rather than diagnosable diseases. A few have used pre-post designs to index changes in general (unspecified) psychiatric functioning.

Assessment procedures range from clinical interviews to standard paper and pencil tests. Furthermore, the sampling range is large, with some studies emphasizing normal populations who undergo stress and then psychiatric decompensation and others emphasizing the decompensation of vulnerable subjects.

Also limiting generalizations are differences in the time frames used for evaluating psychiatric decompensation, which can range from during participation to immediately afterward to an arbitrary 1-year boundary. Intertwined with the differences in time frames is the presumptive argument that if the psychiatric decompensation occurs contemporaneously, a cause/effect relationship can be inferred. The obvious flaw in such reasoning needs little elaboration. A plausible alternative explanation, one that I have seen cases of, is that individuals enter large group awareness training activities as a last desperate effort for rescue and the consequent disappointment may intensify the psychiatric decompensation.

Some authors have pointed to specific processes that are presumed to be characteristic of large group awareness training (14). These processes range from an emphasis on regressive characteristics of the setting to overidentification with the aggressor, the group leader. Beyond retrospective case studies, there is little compelling evidence and less theory implicating particular processes as toxic for specific people.

The present article describes three studies undertaken to determine the effects of participation in large group awareness training on psychiatric status. In the initial study (study 1), 299 participants in a 5-day large group awareness training conducted by Lifespring served as subjects. Study 2 focuses on a new sample from Lifespring's "Advanced Training Course"; 34 (the total N) participants were studied 6 months after completing the course. Study 3 is a 3-year follow-up of those identified in study 1 as potentially at risk.

STUDY 1

Method

One basic Lifespring training session was studied. The training session lasted for 60 hours between a Wednesday evening and the following Sunday. Of the 299 participants, 289 returned usable forms. Fifty-two percent (N=150) were women; 75% (N=217) were between the ages of 20 and 40; only 5% (N=15) were over 50. A large percentage were single (45%, N=130) or separated or divorced (26%, N=75). Participants were generally well educated; only 10% (N=29) had not attended college; 36% (N=104) were currently working on or had completed their postgraduate or professional education.

Three independent methods were used to identify potentially vulnerable participants for clinical study: 1) direct observations during the training, 2) a series of scales administered prior to training that had previously been found to be associated with high risk (10), and 3) a peer-nomination procedure.

Direct observation. The investigators (M.A.L. and I.Y.) moved around the large training room, sitting in small groups, listening to dyads, and monitoring communal activities as well as engaging in informal "conversation" with participants. Risk cues included high conversion, physical and psychological stress responses, bizarre or erratic behavior, and trainer-induced incidents that might be experienced as demeaning or ridiculing. Fifteen participants were identified.

Psychological profiles. Seven scales were administered before training commenced, measuring 1) perceived safety–danger of the upcoming training; 2) attitudes toward experiential education (genuine—phony); 3) "experiencing" and 4) "changing" (two measures of participants' training values); 5) positive/negative self-concept and 6) level of self-esteem (assessments of mental health); and 7) general orientation toward the world, specifically what is perhaps best characterized as a misanthropic view.

The previous study (10) found that those who perceived the experiential learning as totally safe, were uncritically trusting of the circumstances, expected to make miraculous changes, did not value the actual experience itself, had a misanthropic view of their

interpersonal world, had low self-esteem, or had a negative self-concept were more likely at risk. Subjects in the current study received a positive sign on a scale if they scored one standard deviation below the mean score in the risk direction. Fourteen participants had four or more positive signs.

Peer nomination. The single best predictor of subsequent emotional distress was previously found to be peer judgment (10). At termination all participants nominated those who they believed had been overly distressed, hurt, harmed, or disturbed. Seventeen were nominated by three or more people; four others nominated themselves. In all, 30 participants (10%) were selected. They were contacted within 1 week and interviewed during the following 3 to 4 weeks. Three refused to be interviewed; four others moved out of the area. The interview covered the participants' view of their participation; a review of specific behavior during the first week following training, including physiological symptoms indicative of distress; dreams and other fantasy material; and areas of psychological and social functioning in the major role areas, including marital, parental, and occupational.

Results

The clinical interviews revealed no evidence sufficient to classify interviewees as psychiatric "casualties." Casualty criteria were identical to those developed in the previous study (10): the individual is "functioning significantly poorer than [he or she] had prior to the training, . . . the decrement in functioning has some enduring implications in the person's life," and the poor functioning was associated with the group experience. Within the limitations of our methodology, no positive evidence was found that permanent psychological harm to the participants occurred.

The finding that serious casualties did not occur should not be construed as a finding that casualties could not occur in large group awareness training. Evidence that some participants reacted to the training by experiencing high distress was found. Five people showed behaviors indicative of high stress. For example, one who had a history of ulcers developed bleeding directly linked to the training; another experienced what can best be described as a transitory psychotic episode lasting 1½ days; others experienced milder states of disorientation and depression. All of these states, however, were transitory, and within a week or less after training all of the affected participants had reorganized themselves and resumed their previous level of functioning.

STUDY 2

Method

Thirty-eight participants entered the advanced large group awareness training. One participant was asked to leave during the first day because the leader judged that the participant was not ready for the advanced course. Of the 37 who completed, 33 were interviewed 6 months after the training, two people refused, and two others moved out of the area. The 60-hour advanced training was described by participants as more intense and emotionally involving than the basic large group awareness training, and there was a much greater degree of individual tailoring.

The methods used to identify vulnerable subjects in the initial study identified only a small risk pool in study 2. Since these are methods for sample selection, not evidence of psychological harm, an alternate strategy was designed to investigate negative effects.

All participants were evaluated 6 months after completion using a clinical interview similar to that used in study 1. In addition, the Diagnostic Interview Schedule (DIS), a 263-item questionnaire validated to produce a *DSM-III* diagnosis, was administered. The DIS provided information on current psychiatric status as well as estimates of illness over the past 6 months, 1 year, and lifetime. The DIS was scored using the standard computer routine provided by the National Institute of Mental Health.

Results

Diagnosable disorders used in this study included mania, depression, bipolar disorders, schizophrenia, schizophreniform disorders, phobias, somatized psychiatric disorders, and panic disorders. That portion of the DIS assessing substance abuse, antisocial personalities, and cognitive impairment was not administered, since none was expected to be a major new disorder linked to the effects of large group awareness training experience.

Six subjects met the criteria for current psychiatric disorders; three showed patterns of current depressive illness and three were classified as demonstrating phobic illnesses. In addition, four others showed evidence of past depressive and/or phobic disorders but did not meet criteria for a current diagnosis. In all, 10 of the 33 participants showed evidence of diagnosable mental disorder at some point in their lifetimes, but only six evidenced disorders within the past 6 months (the time since training) that met *DSM-III* criteria levels.

All six subjects who met *DSM-III* criteria 6 months after participation demonstrated an identical disorder over their lifetime; there is no evidence that they became psychiatric casualties as a result of their participation. Simply put, those who had experienced psychiatric disorders throughout their adult lifespan manifested those disorders both before and after their participation. It would be difficult to conclude that a causal relationship exists. The records of those who were suffering from diagnosable psychiatric disorders prior to their entrance in the large group awareness training did not indicate any intensification of the disorder following the experience. Conversely, we could not conclude the opposite: that those who met DIS criteria prior to the large group awareness training

but not subsequently were "cured" by their experience.

STUDY 3

Method

The last inquiry was a follow-up of the risk sample described in the first study, 3 years after completion. The goal was to determine whether there were any long-term negative consequences for subjects selected as potentially vulnerable. Of the 33 subjects, only 13 could be located, and of those, two would not agree to be interviewed. The sample was sharply restricted, and we were able to complete clinical interviews with only 11. Despite the reduced sample, the results are of interest because they address an area that heretofore has been inadequately examined: the long-term mental health consequences of large group awareness training.

Results

Both clinical interviews and the DIS were used. Of the 11 people interviewed, three reached criterion levels for current psychiatric diagnosis on the DIS (obsessive-compulsive, phobic, and schizophrenic). All three showed the same lifetime diagnosis. Four others, although not reaching criteria for current diagnosis, did show lifetime designations: two had phobia diagnoses and two had alcohol abuse, one with a secondary diagnosis of dysthymia. Thus, of the 11 interviewed, seven met criterion scores on the DIS for lifetime psychopathology. Clearly, the sample chosen for risk in study 1 comprised people who had a high rate of psychiatric problems at some point in their lives.

The long-term follow-up results do not alter the overall findings. Evidence linking such settings to major psychiatric problems is not available. The DIS scores suggest that a significant minority enter with diagnosable psychiatric disorders that are primarily behavioral and neurotic. There is no evidence from long-term follow-up that such disorders are exacerbated or that persons who have those disorders deteriorate.

The clinical interviews echo these observations. Of the three individuals selected by the DIS as showing current psychopathology, all are presently in serious trouble. All reported numerous exacerbations of their condition over many years, both prior to and subsequent to large group awareness training, and had sought out many other helping settings, including psychotherapy. Currently, they are leading relatively disordered lives, but such disordered lives do not appear to be linked to their participation in large group awareness training.

The interviews with the other participants provide a poignant characterization of the problems of linking particular events such as large group awareness training to the complex, ever changing lives of people. Some participants are now doing very well, compared to 3 years ago. Their lives have stabilized, and some of the problems they described seem well on their way to solution. Some participants provide a clear-cut rationale for how large group awareness training helped change their lives for the better; others who have improved are equally firm in their view that their large group awareness training had little to do with their improvement. Still others maintain that they are vastly improved and their lives are better, yet their portrayals in the current interview and the interview 3 years ago seem identical and troubled to this reviewer.

IMPLICATIONS

The findings from the three studies do not provide positive evidence that large group awareness training settings are inherently risky, even when participants with previous diagnosable pathology are considered. Negative effects were clearly found in the initial study, but such effects were not viewed as causing psychiatric casualties. Without a control group for study, it is difficult to put in context the reaction rates. Whether the five participants (total N=289) who experienced "stress reactions" in the first study would have experienced such stress under other conditions cannot be answered. The clinical evidence, however, is that the reactions were directly attributable to the large group awareness training.

On the basis of the findings of the three studies, it is more than likely that previous reports documenting cases of major psychopathology represent an unknown proportion of casualties mixed together with an unknown number of people who showed prior pathology. Such individuals may enter such settings at a point in their lives of deteriorating mental illness. To what extent the settings contribute to, exacerbate, or speed up such incidents or events cannot be answered by the present study. Clearly, subjective probabilities and attributions by the respondents of what caused them either harm or benefit are open to serious question. Observations in published clinical reports on the content of patients' delusions or hallucinations that centered on the large group awareness training experience are not, in and of themselves, evidence of causal relationships.

The processes used in large group awareness training can be emotionally arousing to some participants; the impact of such emotions was shown in the results of study 1. There is no reason to assume, on the basis of the evidence we have so far been able to gather, that large group awareness training could not create psychiatric risk for some. What is clearly lacking, however, is a coherent theory for linking a set of experiences ordinarily encountered in large group awareness training to the development, exacerbation, or intensification of psychopathology. Emotional intensity, which is the dominant causal element reflected in the literature, is not of itself a known pathogenic factor.

Neither precise measurement nor a well-articulated conceptual base exists for linking the psychology of defense and coping strategies to the processes used in large group awareness training.

To provide more precise answers to the question of how risky these activities, involving large numbers of the population, are, two requirements for investigation need to be met. Sufficiently large samples with good control groups are necessary to calculate risk rates. Also required are clear-cut specifications of the conceptual elements in the processes used in large group awareness training that would permit the examination of the linkage between posttraining psychological state and experiences in the settings.

I am not convinced on the basis of the results that such studies are a high priority. The general impression that I have been left with in studying and observing these groups is that they pose minimal risk, although clearly they are not risk free. Evidence that would permit the identification of people at risk prior to the pathological response is currently not available. Given the logistic difficulties and the absence of a clear conceptual base, the contributions of such studies to furthering our understanding of pathology and its environmental contributors are limited.

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Cerebellar Atrophy in Schizophrenia and Affective Disorder

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The authors evaluated 108 patients with schizophrenia, 50 patients with affective disorder, and 74 age- and sex-matched control subjects by CAT scan for evidence of global cerebellar atrophy. No difference was found between control subjects and schizophrenic patients or between control subjects and patients with affective disorder. This study does not confirm previous reports linking cerebellar atrophy to schizophrenia.

(Am J Psychiatry 1987; 144:465–467)

The computerized tomographic evaluation of cerebellar anatomy in psychiatric patients has been of research interest since the original report by Weinberger et al. (1) of cerebellar vermian atrophy in schizophrenia. Nasrallah and Coffman (2) summarized the current status of this subject by reporting the results of seven studies of CAT scan cerebellar findings in psychiatric patients. Four of these studies revealed an increase in cerebellar atrophy in schizophrenia; Heath et al. (3) reported that up to 40% of schizophrenic patients had vermian atrophy. Nasrallah et al. (4, 5) conducted two studies suggesting a trend toward increased atrophy in schizophrenic patients compared with control subjects, but these findings did not reach statistical significance and would therefore be considered negative studies. Finally, a CAT scan study by Coffman et al. (6), who used a cross-sectional vermian area, found no difference between schizophrenic patients and control subjects. Consonant with this negative finding in a CAT scan study is a recent report that magnetic resonance imaging failed to find significant cerebellar changes in schizophrenia (7). The psychiatric population with reported cerebellar anatomical changes was extended to patients with bipolar affective disorder in a study in which 27% of a small group of bipolar patients were found to have evidence of cerebellar atrophy (4). Our purpose in this study was to compare cerebellar atrophy in a large group of patients with schizophrenia or affective disorder with a matched control population.

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Supported in part by NIMH grant MH-31593, a Scottish Rite schizophrenia research grant, the Nellie Ball Trust Fund, and grant RR-59 from the General Clinical Research Centers Program, Division of Research Resources, National Institutes of Health.

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METHOD

One hundred eight patients with schizophrenia, 50 patients with affective disorder (24 bipolar, 26 unipolar), and 74 control subjects were evaluated by CAT head scan. The patients were inpatients at the University of Iowa Psychiatric Hospital who met *DSM-III* criteria for their respective disorders and gave informed consent before scanning. The control subjects were matched in sex and by decade for age to the psychiatric patient sample; they also gave informed consent.

The schizophrenic patients had a mean±SD age of 31.7±10.4 years, a mean educational level of 12.7± 2.4 years, a lifetime duration of hospitalization of 19.6±43.8 months, and a total of 4.5±4.4 hospitalizations. Sixty-five were men and 43 were women, 28 had received ECT at some time in the past, all had been treated with neuroleptics, eight met *DSM-III* criteria for substance abuse, and 15 met *DSM-III* criteria for alcohol abuse. The bipolar patients had a mean age of 35.5±14.3 years, a mean educational level of 12.2± 8.5 years, and a total of 5.8±4.7 hospitalizations. Twelve were men and 12 were women, 11 had received ECT at some time in the past, 19 had been treated with neuroleptics, one met *DSM-III* criteria for substance abuse, and two met *DSM-III* criteria for alcohol abuse. The unipolar subjects had a mean age of

TABLE 1. Cerebellar Atrophy in Patients With Schizophrenia and Affective Disorder and Age- and Sex-Matched Control Subjects

	Less Than 50 Years Old			50 Years Old or Older			Total		
		Cerebellar Atrophy			Cerebellar Atrophy			Cerebellar Atrophy	
Subjects	N	N	%	N	N	%	N	N	%
Control subjects	60	2	3.3	14	0	0.0	74	2	2.7
Patients with schizophrenia	101	4	4.0	7	0	0.0	108	4	3.7
Patients with bipolar affective disorder	19	0	0.0	5	2	40.0[a]	24	2	8.3
Patients with unipolar affective disorder	23	0	0.0	3	0	0.0	26	0	0.0

[a]Trend toward difference from elderly control subjects (p=.069, Fisher's exact test, one-tailed).

37.3±13.3 years, a mean educational level of 13.4± 3.1 years, a lifetime duration of hospitalization of 6.2±8.2 months, and a total of 3.6±3.5 hospitalizations. Twelve were men and 14 were women, 13 had received ECT at some time in the past, none met *DSM-III* criteria for substance abuse, and three met *DSM-III* criteria for alcohol abuse.

CAT scanning was done by using a Picker 600 CT Scanner (8) with a resolution power in the 1 mm range, dependent on tissue type and density. The cerebellar atrophy rating was done by using a scale from 0 to 3 (0=absent, 1=mild, 2=moderate, 3=severe). Atrophy ratings were done by a neuroradiologist with previous experience in research rating of cerebellar atrophy (C.G.J.). These ratings were done on a group of CAT scans screened by a psychiatric resident (W.R.Y.) for any evidence of atrophy. The criteria for cerebellar ratings have been described elsewhere (4). Briefly, for atrophy to be considered present, at least one or more of the following criteria were necessary: 1) a cerebellar hemisphere sulci larger than 1 mm, 2) two or more cerebellar vermian sulci enlarged, 3) cerebellopontine cistern enlarged, 4) superior cerebellar cistern enlarged, and 5) fourth ventricle enlarged. If only one criterion was present and borderline in interpretation, atrophy was considered absent. Since no subjects met criteria for moderate or severe cerebellar atrophy, the diagnostic groups were compared by the presence or absence of cerebellar atrophy by chi-square analysis with Yates' correction or by Fisher's exact test when expected values were less than 3 in any cell.

RESULTS

Four schizophrenic patients showed evidence of mild cerebellar atrophy (table 1). This was not significantly different for the control group, in which two patients had mild atrophy. Two patients with affective disorder, both bipolar and older than 50 years of age, had cerebellar enlargement. The overall rate of enlargement was not different in the patients with affective disorder when compared with control subjects, although there was a trend for the elderly bipolar patients to differ from elderly control subjects (table 1).

Because of the previous link of alcohol abuse and ECT to cerebellar atrophy, we reanalyzed the results excluding patients who had received ECT or who had been diagnosed as having alcohol abuse. Normal subjects had been screened with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) interview (9) and were excluded if any history of ECT or alcohol abuse was present. In the analysis of patients without a history of ECT or alcohol abuse, three of 72 schizophrenic patients had atrophy, compared with two of 74 control subjects (Fisher's exact p=.486, one-tailed). The previous trend toward cerebellar atrophy in the elderly bipolar group persisted when patients with ECT and alcohol abuse were excluded; two of three elderly bipolar patients demonstrated atrophy, compared with none of 12 control subjects (Fisher's exact p=.029, one-tailed).

DISCUSSION

To our knowledge, this is the largest psychiatric patient sample to have been evaluated for evidence of cerebellar atrophy by CAT scan. The finding of atrophy in 2.7% of control subjects compares well to the finding of Koller et al. (10) that only 2.5% of normal control subjects under 60 years old had evidence of cerebellar atrophy. The negative finding in patients with schizophrenia compared with control subjects supports the previous negative findings of Nasrallah et al. (4, 5) and Coffman et al. (6) but differs from the several previous positive findings in schizophrenia. Our findings also do not support the finding of cerebellar atrophy in young men with bipolar disorder (ages 25–45 years) (4), although this study supports atrophy in elderly bipolar patients.

Our results suggest that patients with schizophrenia and affective disorder do not differ from control subjects in global estimates of cerebellar atrophy. Comparisons between our findings and previous positive findings are made difficult because of different methodologies. Our global estimates consider several measures of cerebellar atrophy in making a rating. A borderline finding in only one measure was not sufficient for qualification of atrophy because of the inherent limitation of scanning techniques and normal variability. Previous studies linking cerebellar changes to schizophrenia have often focused on vermian atrophy alone or have treated a single indicator as sufficient for making a positive global rating. The global

estimate method is more consistent with routine neuroradiologic interpretation in clinical radiology.

An additional methodological point should be made. If there is a true difference in cerebellar atrophy in subsets of psychiatric patients, and if this difference is subtle enough to approach the limits of CAT scan precision, then scanning techniques and the method of estimation of atrophy become even more important in interpreting results. An additional statistical point is relevant in interpreting these findings. Extremely large sample sizes are necessary to determine statistically significant differences between groups in whom the rate of the phenomenon studied is small (i.e., less than 10%) in both groups at baseline. If we assume that the rate of cerebellar atrophy is 3% in control subjects and 6% in patients with schizophrenia, then a sample size of nearly 400 patients would be necessary to detect significant differences between the groups using chi-square analysis. Such large sampling is difficult to obtain.

Because it is large and representative, we believe our sample may provide an accurate estimate of the rate of cerebellar atrophy in schizophrenic patients and control subjects. Differences between our negative findings and the positive findings of other studies could reflect differences in sample selection, with varying effects of confounding variables such as age, alcohol abuse, and ECT use. Given the statistical qualifications mentioned, our results must be interpreted conservatively. Nevertheless, the results may indicate that young nonchronically ill patients with schizophrenia, bipolar illness, and major depression do not suffer cerebellar atrophy.

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Induction of Depression With Oxotremorine in Patients With Alzheimer's Disease

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Cholinergic neurotransmission has long been implicated in the development of depression. In this study seven patients with Alzheimer's disease were given oral oxotremorine, a long-acting cholinergic agonist, to assess the drug's effects on cognitive function. There were unexpected depressive reactions in five of the seven patients; three patients dropped out of the study because of these side effects. Cardiovascular effects of the drug were negligible, but its effect on memory and cognition remains unknown because of the small number of subjects who completed the study.

(Am J Psychiatry 1987; 144:468–471)

The cholinergic system has been implicated as the source of the major neurotransmitter abnormality in Alzheimer's disease. Neurochemical studies of brains of patients with Alzheimer's disease demonstrate large reductions of choline acetylcholinesterase activity in the cortex and hippocampus (1–3), which is due in part to selective degeneration of cholinergic neurons originating in the nucleus basalis of Meynert (4). The reduction of choline acetylcholinesterase activity in these brain areas is quantitatively correlated both with numbers of neuritic plaques and with severity of dementia (5). In parallel with reductions in choline acetylcholinesterase activity, the number of M_2 cholinergic receptors in the brains of patients with Alzheimer's disease is also diminished (6). Cortical M_1 receptors may be located in postsynaptic sites and facilitate cellular excitation, whereas M_2 receptors may be presynaptic receptors. The likelihood that postsynaptic cholinergic receptors remain relatively intact encourages the use of cholinergic agonists in the treatment of dementia, particularly because the efficacy of this strategy is independent of the integrity of the cholinergic neuron. Thus, we treated seven patients who had Alzheimer's disease with the experimental cholinergic agonist oxotremorine in an attempt to improve their memory and cognition. To our surprise, these patients experienced striking depressive symptoms.

Cholinergic transmission has long been thought to have a key role in the development of depression. Manic-depressive illness has been viewed as an imbalance between the cholinergic and noradrenergic systems, with depression associated with increased cholinergic activity and mania with increased noradrenergic activity (7–11). Cholinergic agents such as physostigmine, an acetylcholinesterase inhibitor, and diisopropylfluorophosphate, an irreversible cholinesterase inhibitor insecticide, have been noted to cause depression in normal subjects (12, 13) and manic patients (10, 14, 15) and to exacerbate symptoms in depressed patients. A number of other clinical studies support the cholinergic hypothesis of affective illness (16, 17), and an increased density of muscarinic cholinergic receptors on fibroblasts has been shown to be associated with a vulnerability to affective disorders in some families (18), although these findings have not been replicated (19). While there are data which indicate that cholinergic mechanisms such as receptor supersensitivity underlie some affective symptoms, previous studies of intravenous (20) and oral (21) physostigmine in patients with Alzheimer's disease, at doses selected to enhance memory, did not report the production of affective symptoms. Hence, the induction of depressive symptoms with oxotremorine was not considered likely, although oxotremorine differed from these previous drugs in that it is a long-acting direct cholinergic agonist.

METHOD

Each of the seven patients we studied met rigorous criteria for the clinical diagnosis of Alzheimer's disease, and scores on autopsy-validated rating scales such as the Memory and Information Test (22), the

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Supported in part by NIH grant RR-71 from the Division of Research Resources, General Clinical Research Centers Branch; a grant from the Medical Research Service of the Veterans Administration; and U.S. Public Health Service grants AG-02219 and AG-05138 from the National Institute on Aging.

TABLE 1. Reactions to Oxotremorine of Seven Patients With Alzheimer's Disease

Patient	Sex	History of Alzheimer's Disease: Age (years)	Length (years)	Severity	Dose of Oxotremorine (mg)	Side Effects
1	M	63	6	Mild	0.5	Sad, felt like crying, didn't know why he was depressed, teary
					1.0	Sad, crying, didn't know why he was still emotional about daughter dying after giving birth
2	F	78	6	Moderate	0.5	Dizzy, pale, chills, diaphoretic, "dull, no energy," tearful
3	F	70	6	Mild	0.5	Very agitated, visibly upset, cried hysterically
					1.0	Depressed, irritable, felt sorry for herself, cried intermittently
4	M	58	3	Severe	1.0	Dizzy, nervous
					2.0	Weeping, anxious, dizzy
5	M	62	2.5	Moderate	1.0	Weak, pale, dizzy, abdominal pain, anxious, confused
6	M	57	5	Severe	1.5	Dizzy, urge to defecate, disoriented, agitated, sad, wanted to call wife
7	M	66	4	Severe	0.5	Pale, cold, diaphoretic, bradycardia, hypotension

TABLE 2. Results of Cognitive Testing of Seven Patients With Alzheimer's Disease Who Received Oxotremorine

Patient	Baseline Test Score: Memory and Information Test	Blessed Scale	Hachinski Ischemic Scale	Alzheimer's Disease Assessment Scale	Replication Phase Condition (Oxotremorine or Placebo)	Word Recognition Test Score[a]: 11:00 a.m.	3:00 p.m.	8:00 p.m.	9:00 a.m.	Mean
1	16	9	0	18.0	Placebo	20	20.7	22.7	22.3	21.5
					Drug, 1.0 mg	21.3	19.7	22.0	21.3	21.1
2[b]	7	13	0	26.1						
3	12	12	0	26.6	Drug, 0.5 mg	18.0	14.7	15.0	14.7	15.6
					Placebo	14.3	15.3	15.3	16.7	15.4
4	2	25	1	45.7	Placebo	17.7[c]	—	—	—	—
					Drug, 2.0 mg	19.3[c]	—	—	—	—
5[b]	9	—	1	—						
6	14	13	0	41.8	Drug, 0.5 mg	13.7	17.7	18.7	14.7	16.2
					Placebo	20.7	16.7	19.3	19.0	18.9
7[b]	9	11	2	44.3						

[a]A higher score on the word recognition test denotes improvement.
[b]Patient did not complete study because of side effects.
[c]This patient was tested only at 11:00 a.m.

Dementia Rating Scale (23), the Blessed Scale (23), and the Hachinski Ischemic Scale (24) were used in conjunction with strict inclusion and exclusion criteria to improve diagnostic accuracy. Patients were also assessed with the Alzheimer's Disease Assessment Scale (25). Although the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) report on the diagnosis of Alzheimer's disease (26) was published after patients had been selected for this study, all the patients met criteria for the NINCDS diagnosis of probable Alzheimer's disease. Informed consent was obtained from all patients and/or their spouses.

Each patient received a single dose of placebo and 0.25 mg, 0.5 mg, 1.0 mg, 1.5 mg, and 2.0 mg of oxotremorine in random order and under conditions to which the patient and staff, with the exception of one physician, were blind. The doses were given at 8:30 a.m. at 3–10-day intervals during a "dose-finding phase," the purpose of which was to select the dose that yielded maximal improvement on cognitive testing. This was followed by a replication phase in which the individualized, previously determined "best dose" of oxotremorine was compared to placebo in a double-blind manner. The interval between doses was determined by the day of the week, the occurrence of weekends, the convenience of the patient, and the availability of staff. Twenty minutes before and 45 minutes after receiving oxotremorine, the patients received propantheline bromide, 1.25 mg i.v., to prevent peripheral cholinergic side effects. Two hours after oral administration of the oxotremorine or placebo dose, each patient was given a word recognition test (27).

RESULTS

We describe the affective and cognitive effects of oxotremorine on these patients in the following case report and in tables 1 and 2. Table 1 summarizes the side effects for each patient. Briefly, two patients who

received only low doses of oxotremorine reported feeling anxious. The remaining five patients reported depressive reactions ranging from tearfulness, irritability, and feeling sad to open weeping, lasting up to 8½ hours, with intermittent crying episodes the next morning. There were no consistent changes in the subjects' blood pressure and pulse, and peripheral cholinergic symptoms could be reversed with intravenous propantheline bromide. Table 2 summarizes the results of cognitive testing on word recognition of the four patients who completed the replication phase; three patients did not complete the study because of the side effects they experienced.

CASE REPORT

Case 1. Mr. A, a 63-year-old married, retired executive, had a 5–6-year history of slowly progressive deterioration of memory, with only minimal disturbance of speech and praxis. He had no past or family history of major depression and no current symptoms of depression. Following doses of placebo and oxotremorine, 0.25 mg, the patient had no complaints. Three hours after receiving 0.5 mg p.o. of oxotremorine, Mr. A stated that he felt sad, had not felt this sad in a while, and did not know why he felt this way. Three and one-half hours after the 0.5-mg dose, he stated that he was "suddenly depressed," became teary, and began crying profusely, saying that he did not know why he was crying. Four hours after the 0.5-mg dose, he was no longer depressed but feeling sleepy. After consulting with Mr. A's family, we decided to try a higher dose of oxotremorine, since other treatment options for his dementia were limited and since the depressive symptoms that we had observed might have been idiosyncratic for that dose and not another dose or might have been unrelated to cholinergic enhancement. Furthermore, the depressive symptoms were self-limited and posed no long-term risk, whereas the dementia was chronic and resulted in considerable morbidity.

When given a 1.0-mg dose of oxotremorine, Mr. A became severely depressed after 45 minutes, with profuse crying, and stated that he was emotional about the fact that his daughter had died after giving birth several years earlier. These depressive symptoms lasted for 4 hours. There was no significant improvement in word recognition on cognitive testing of this patient. No significant change in blood pressure or pulse was noted.

DISCUSSION

Oxotremorine was found to have significant side effects in our sample of patients with Alzheimer's disease. In particular, depressive symptoms—often severe—were present in five of the seven patients and appeared to be dose dependent; the more severe depressive symptoms occurred 1–5 hours after the higher doses. No assessments of patients on depression rating scales were formally included in this study because, on the basis of previous experience with physostigmine in Alzheimer's disease, affective symptoms were not anticipated. However, the study design included a placebo-controlled, double-blind replication phase and a placebo dose during the dose-finding phase, and no patients developed an affective reaction while receiving placebo. Even the two patients who were not noted to be depressed became anxious and confused following administration of oxotremorine. It is known that certain neurological lesions may result in aprosodia or the distortion of certain salient features in the expression of depression or emotion (28, 29), and thus these symptoms might be depressive equivalents.

Although the cholinergic hypothesis of affective illness is well known, and cholinergic agents have been correlated with depressive symptoms in normal subjects and depressed and manic patients (7, 9–11, 18), this study found important depressive symptoms in patients with Alzheimer's disease who were treated with oxotremorine, a long-acting muscarinic receptor agonist. This is in marked contrast to results obtained in studies using oral and intravenous physostigmine for such patients (20, 30), in which no depressive symptoms were noted. The severity of the affective response after administration of oxotremorine may be related to the tonic rather than the phasic nature of receptor agonists compared with presynaptic and synaptic agents and their differential action on M_1 and M_2 muscarinic receptors. While presynaptic agents such as acetylcholinesterase inhibitors or releasers (e.g., 4-aminopyridine) may increase synaptic acetylcholinesterase in a phasic manner more physiologically equivalent to that of the intact neuron, agonists such as oxotremorine may stimulate receptors in a prolonged and tonic manner, which may be related to the drug's severe depressive side effects. In the cortex the M_1 receptor is thought to be a postsynaptic receptor, while the M_2 receptor may be a presynaptic autoreceptor (19). The depressive side effects of muscarinic agonists may be mediated by the M_1 receptor, and since their memory-enhancing properties may also be mediated by this same receptor, this may limit the potential utility of these agents.

Contrary to recent reports (30), no significant increase in blood pressure or pulse was noted in our patients with Alzheimer's disease following administration of this cholinergic agonist, despite the increased central cholinergic activity that was manifested by the depressive side effects. Because of these side effects, only four patients completed the study, and thus the role of a cholinergic agonist in enhancing memory and cognition in Alzheimer's disease remains untested. However, the development of depression in patients with Alzheimer's disease after administration of oxotremorine does provide additional support for the role of cholinergic mechanisms in depression.

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DST and TRH Stimulation Test in Mood Disorder Subtypes

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Both the dexamethasone suppression test (DST) and the thyrotropin-releasing hormone (TRH) stimulation test have been reported to be useful in subtyping some depression diagnoses. Whether the DST discriminates delusional from nondelusional depression remains controversial, but this possibility has not been studied for the TRH test. The authors evaluated DST and TRH test results in 29 depressed hospitalized patients; both tests significantly discriminated patients with nonendogenous depression from those with endogenous depression. Furthermore, postdexamethasone cortisol levels but not the change in thyroid-stimulating hormone discriminated the patients with endogenous delusional depression from those with endogenous nondelusional depression.

(Am J Psychiatry 1987; 144:472–475)

In the past several years, many investigators have used the dexamethasone suppression test (DST) and the thyrotropin-releasing hormone (TRH) stimulation test in an attempt to subtype patients with major depression. Unfortunately, the results have been conflicting; some (1–4) but not all (5) investigators have reported that patients with endogenous depression have a higher rate of cortisol nonsuppression on the DST than those with nonendogenous depression. Similarly, some groups have found postdexamethasone cortisol levels to be particularly high in delusionally depressed patients (6, 7), but others have been unable to replicate this finding (8, 9). With regard to the TRH test, most (4, 10, 11) but not all (12) researchers have found a blunted thyrotropin-stimulating hormone (TSH) response to TRH to be more common in patients with endogenous depression. The possible utility of the TRH test to distinguish delusional from nondelusional depression has not been well studied.

Several factors may contribute to the disparity of results with these tests. Some studies evaluating delusional and nondelusional depression have not specified how many of the nondelusional patients were suffering from endogenous depression and how many from nonendogenous depression. Variations in this proportion conceivably could affect the findings. Ritchie et al. (13) have suggested that each laboratory validate its own cortisol criterion for nonsuppression on the DST. An arbitrary cutoff of 5 μg/dl may fail to yield appropriate test specificity and sensitivity, because varying cortisol assays are used by different laboratories. Thus, the lack of independently validated postdexamethasone cortisol cutoff values may account for some of the discrepant results reported in the literature.

No study, to the best of our knowledge, has examined the rates of both DST nonsuppression and TSH blunting in a sample of well-defined unipolar depressed patients that includes a delusional subtype. The possibility that both the DST and the TRH stimulation test may discriminate subtypes of endogenous depression either alone or together was the impetus for this investigation.

METHOD

All patients at least 18 years of age who were admitted to the inpatient Mood Disorders Program at the Ohio State University Hospitals were diagnosed by Research Diagnostic Criteria (RDC) (14). Patients meeting RDC for major depression without history of schizophrenia, mania, hypomania, or substance abuse were accepted into this study. Patients with a history or evidence of an endocrinopathy or who were taking medication known to interfere with DST or TRH test results were excluded from the study. Patients taking antidepressants were included in the study, since these drugs have been found not to interfere with either test (1). Subjects were excluded if they had been withdrawn from a medication with anticholinergic activity within 2 weeks of admission, since anticholinergic effects may affect DST results (15).

Our study group consisted of 29 patients (10 men and 19 women), who were studied within 3 days after admission. RDC diagnoses and ratings on the 17-item Hamilton Rating Scale for Depression were determined before the neuroendocrine studies were conducted. Eight patients (four men and four women) had

Received Nov. 22, 1985; revised April 16 and July 14, 1986; accepted Sept. 10, 1986. From the Mood Disorders Program, Department of Psychiatry, Ohio State University. Address reprint requests to Dr. Levy, Department of Psychiatry, Ohio State University, 473 West 12th Ave., Columbus, OH 43210.

The authors thank Don Smeltzer for statistical assistance and Julie Luzny for manuscript preparation.

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TABLE 1. Neuroendocrine Profiles of 29 Patients With RDC Depression

Depression Diagnosis	T_4 (μg/dl)		Peak Postdexamethasone Cortisol Level (μg/dl)		Abnormal Test Results[a]							
					DST		TRH		Both		Either	
	Mean	SD	Mean	SD	N	%	N	%	N	%	N	%
Nonendogenous (N=8)	7.2	3.0	2.1	1.1	0	0	0	0	0	0	0	0
Endogenous (N=21)												
Nondelusional (N=13)	8.5	1.2	6.8	5.1	8	62[b]	8	62[b]	6	46[e]	10	77[d]
Delusional (N=8)	9.3	1.6	12.6[c]	6.2	7	88[d]	4	57[e]	4	57[e]	7	88[d]

[a]DST, cortisol>5 μg/dl; TRH, TSH<7μU/ml.
[b]Significantly different from nonendogenous (Fisher's exact test, p=.01).
[c]Significantly different from nonendogenous (F=8.68, df=27, p<.005).
[d]Significantly different from nonendogenous (Fisher's exact test, p=.001).
[e]Significantly different from nonendogenous (Fisher's exact test, p=.03).

nonendogenous major depression; among the 21 patients with endogenous major depression, 13 (five men and eight women) were nondelusional and eight (one man and seven women) were delusional.

The TRH test was performed at 8:00 a.m. after patients had been at bedrest and had fasted overnight. Serum samples for TSH determination were drawn just before and 30 minutes after an intravenous infusion of 500 μg of TRH over a 1-minute period. The ΔTSH was the difference between the 30-minute and the baseline TSH level.

Dexamethasone, 1 mg, was given at 11:00 p.m. the night after the TRH test. Serum was drawn the following day at 4:00 p.m. and 10:00 p.m. for cortisol analysis. All cortisol and TSH samples were analyzed within 2 hours of being drawn.

TSH was analyzed by radioimmunoassay at the Ohio State University Endocrinology Laboratory. At a TSH level of 8.9 μU/ml, the interassay and the intra-assay coefficients of variability are 5.2% and 1.8%, respectively; at a TSH level of <2 μU/ml, the interassay and intra-assay coefficients of variability are 8.2% and 4.1%, respectively. Cortisol was analyzed in the same laboratory by radioimmunoassay; "Gammacoat" ^{125}I-cortisol (manufactured by Travenol-Genetech Diagnostics) was used. At a cortisol level of 3.8 μg/dl, the interassay and intra-assay coefficients of variability are 9.7% and 7.9%, respectively. Neuroendocrine tests were considered to be abnormal if at least one postdexamethasone cortisol level was >5 μg/dl or if the ΔTSH was <7 μU/ml.

Differences among group means were analyzed by means of an analysis of variance (ANOVA). Fisher's exact statistics were used in evaluating differences in DST results between groups at various cortisol cutoff levels.

RESULTS

Although many patients were taking antidepressants, they were distributed among the diagnostic groups, i.e., 25%–50% of the patients in each group were drug free. The small number precluded our determining whether patients taking medication differed from those who were medication free. However, others (1) have claimed that these neuroendocrine test results are not altered by antidepressants.

The delusional patients were older (mean±SD age= 57.8±12.9 years) than the nonendogenous(44.3±11.7 years) or endogenous nondelusional (46.9±16.6 years) patients, but this difference was not statistically significant. There was a significant group difference in Hamilton scale scores: patients with delusional depression manifested a significantly higher mean±SD score (30.6±3.1) than those with nonendogenous depression (F=8.05, df=28, p<.005; Scheffé procedure, p<.05).

The neuroendocrine results for our three diagnostic groups of depressed patients are given in table 1. There was a significant group difference for the maximum postdexamethasone cortisol level. Patients with delusional depression had a significantly higher postdexamethasone cortisol level than patients with either endogenous nondelusional depression or nonendogenous depression (Scheffé procedure, p<.05 in both cases). A significantly greater frequency of cortisol nonsuppression (postdexamethasone cortisol>5 μg/dl) was found in the patients with endogenous nondelusional and endogenous delusional depression than in the nonendogenous depressed patients. There was no difference in the rate of nonsuppression between delusional and nondelusional endogenous patients. However, six of eight delusionally depressed patients had a maximum postdexamethasone cortisol level of >11 μg/dl compared to only three of 13 endogenous nondelusional patients (Fisher's exact test, p<.05).

Although there were no significant group differences for mean ΔTSH, the three groups demonstrated a significantly different rate of TSH blunting. There was no difference between delusional and nondelusional endogenous depression in the rate of TSH blunting, but both groups of endogenous patients had more frequent TSH blunting than did nonendogenous patients. This could not be explained by altered thyroid hormone status; T_4, determined by radioimmunoassay, was similar for all groups. A linear regression analysis between T_4 and ΔTSH revealed no association (R=−.242, p=.25).

DISCUSSION

These preliminary findings add to the expanding literature suggesting that the DST and the TRH test may be able to discriminate nonendogenous from endogenous depression. The demonstration of higher postdexamethasone cortisol levels in endogenous delusional patients than in endogenous nondelusional patients supports the position that delusional depression may differ from other depressions biologically as well as clinically.

Schizophrenia has been generally demonstrated to be associated with normal DST and TRH stimulation test results (2, 10); thus, psychosis alone cannot account for the hypothalamic-pituitary-adrenal (HPA) axis abnormalities. Schatzberg et al. (16) made the intriguing suggestion that high cortisol levels in patients with depression may, by activating the dopaminergic system, lead to the development of psychotic symptoms. This indeed may explain the high postdexamethasone cortisol levels seen in psychotic depression but not demonstrated in either nondelusional depression or schizophrenia.

An alternative explanation may be that psychosis in the face of depression is a potent disrupter of the HPA axis but not the hypothalamic-pituitary-thyroid axis. Evidence is emerging to suggest that basal ACTH levels are high in major depression but that the response of ACTH to corticotropin-releasing hormone (CRH) is blunted (10). This indicates that the pituitary is responding to the feedback inhibition of elevated cortisol, but that CRH production is overriding this feedback, resulting in hypercortisolemia. Patients with a delusional depression may produce even more CRH than patients without delusions, thus further overriding the feedback inhibition from endogenous or exogenous (e.g., dexamethasone) corticosteroids.

The HPA disruption does not, however, appear to be explained by the severity of depression in our patients. Although our patients with delusional depression had higher Hamilton depression scale scores, there was no significant relationship between Hamilton scale scores and postdexamethasone cortisol levels, either in delusional or nondelusional patients with endogenous depression. This finding is consistent with the reports of other investigators (17), who found no association between severity of illness and DST results. Some investigators have reported an association between severity of depression and nonsuppression (unpublished data, 18); thus, further investigation is warranted.

Hypothalamic-pituitary-thyroid abnormalities may be governed by somewhat different mechanisms. Loosen and Prange (10) have suggested that the blunted TSH response to TRH in endogenous depression may occur as a result of down regulation of the pituitary due to elevated TRH concentrations. It is not clear, however, if this blunted response represents receptor subsensitivity from increased TRH or, rather, enhanced negative feedback from subtle increases in circulating thyroid hormone. Although there were no significant differences in T_4 levels among our three groups, measurable changes in thyroid hormone may not be necessary to influence TSH response to TRH (19). It is possible that TSH is influenced more by thyroid hormone levels than by TRH. Thus, even if TRH release is enhanced in delusional depression, it may not be sufficient to have any additional effect on TSH responsivity.

In our study sample, most of the delusionally depressed patients were older women. Although sex differences have not been shown to contribute to DST abnormalities, some authors (3, 17) have reported a positive correlation between age and the rate of nonsuppression. We did not find an association between age and postdexamethasone cortisol levels, but investigators who do not carefully screen for psychosis among endogenously depressed subjects may identify an age effect by including a substantial number of older, delusionally depressed patients.

In our sample, the TRH stimulation test discriminated between endogenous and nonendogenous depression nearly as well as the DST did. Unlike the DST, however, the TRH test did not afford further discrimination between delusional and nondelusional endogenous depression. Somewhat more delusional than nondelusional depressed patients had both neuroendocrine abnormalities, but this was not a statistically significant finding.

These results suggest that both the DST and the TRH test may discriminate between nonendogenous and endogenous depression among inpatients. They further suggest that the DST may distinguish delusional from nondelusional endogenous depression at a cortisol cutoff of 11 μg/dl or when the peak level of postdexamethasone cortisol is used. In our study, only three patients had postdexamethasone cortisol levels >17 μg/dl, and they all had delusional depressions.

The possibility that nonsuppression on the DST or postdexamethasone cortisol levels may be higher in delusional depression strongly argues for the identification of this diagnostic subtype in further studies evaluating neuroendocrine abnormalities in endogenous depression. Evidence suggests that patients with delusional depression respond less well to tricyclic antidepressants alone than do individuals with nondelusional depression (8, 20) and that delusionally depressed patients may have a higher familial prevalence of depression (8). Emerging data on neuroendocrine differences in delusional depression, including our results, suggest the need to control for delusional depression in future studies investigating endogenous depression.

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The office of the three APA periodicals, the *American Journal of Psychiatry, Hospital and Community Psychiatry,* and *Psychiatric News,* will be in room L-12 in the Chicago Convention Center. The office will be open Sunday, May 10, 10:00 a.m.–5:00 p.m., and Monday–Thursday, May 11–14, 8:00 a.m.–5:00 p.m.

The *American Journal of Psychiatry* does not have first refusal rights for any papers presented at the annual meeting. However, the *Journal* welcomes the submission of annual meeting papers, which should be in final form and conform to the requirements in "Information for Contributors" (in most issues and available on request). Questions should be directed to the *Journal*'s editorial office at APA (202-682-6020).

Hospital and Community Psychiatry welcomes the submission of material from the annual meeting. The journal publishes clinical, research, and administrative material of interest to professional staff members in mental health facilities and agencies. Papers may be submitted singly, or papers from symposia or paper sessions may be submitted as a group for consideration as a special section. Material must be in final form, ready for blind peer review, and must be in an electronically scannable typeface. Details are given in *H&CP*'s "Information for Contributors," published in the January 1987 issue, and are available from the *H&CP* editorial office at APA (202-682-6070).

Staff of both journals will be available to answer authors' questions. Both journals publish only original material that has not been published elsewhere in any form and that is not being considered for publication elsewhere. Four copies are required for either journal.

The staff of *Psychiatric News* will meet daily in the office to discuss news coverage of the meeting. Persons who wish to contact members of the staff may leave messages to arrange appointments or may leave written announcements or letters for possible publication in the newspaper.

Should Young Children Testify in Cases of Sexual Abuse?

Alayne Yates, M.D.

Children as young as age 3 are testifying in cases of sexual abuse and molestation. Very young children can accurately recall emotionally charged, personally significant events. They demonstrate more errors of omission, difficulties with time and number of concepts, and occasional misinterpretations of others' actions. Children's testimony can be influenced by an overly authoritative or ingratiating attorney stance, an attorney's preconceived notions, age-inappropriate questions, and the child's limited attention span. Children may be helped or harmed by testifying. The risk of further traumatization can be minimized through the judge's use of discretionary power, inclusion of professionals trained in child development in the investigative and court process, and use of videotaping or one-way screens.

(Am J Psychiatry 1987; 144:476–480)

Children at 3 to 7 years of age are now testifying before the criminal court in cases of sexual abuse, rape, and molestation. On the basis of the sixth amendment to the U.S. Constitution, the accused has the right to be confronted by the accuser, whether the accuser is a child or an adult. Prosecution is often impossible if children are barred from testifying. Thus, for justice to be served, the child must appear in court and face the defendant, regardless of how traumatic this might be for the child. In contrast to the protection afforded the accused, the child witness has no constitutional rights to protection during either the investigation or the trial, in spite of the harm already inflicted and the trauma the child may suffer through further legal involvement (1). In some cases, procedural assault is added to sexual assault (2).

Children may also be asked to testify in the probate court on matters of custody or visitation. In this area, the validity of the child's statements is likely to be questioned. There is now ample evidence that the child's word is not always trustworthy, whether by the child's intent to vilify the accused or by the child's unintentional acting out of another person's wish to accuse (3, 4). Many accusations of sex abuse that occur in the course of custody disputes are inaccurate. For instance, one young mother accused her ex-husband of molesting their 4-year-old daughter because he took showers with her in the nude. The child can be drawn into a fabrication through devious means. In one case, for example, a mother asked her 5½-year-old daughter, "Don't you remember all the times when daddy rubbed your tushy? You *don't?* It was when we lived in the house down on the lake and you thought it was such a funny game and he liked to do it so much—oh, you *must* remember that!" After several additional variations on the same theme, the little girl thought that her father had rubbed her "tushy" and even imagined how it must have felt. She was embarrassed about having forgotten such a significant event. The truth came to light when the defense attorney asked the child if she had really remembered the events or if her mother had needed to remind her of them. Had it not been for that astute attorney's question, the father would not have been allowed visitation and could have been sent to the state prison.

Whether it is proper for 3- to 7-year-old children to testify depends on two factors. The first is whether the child has sufficient cognitive skill (competency) and memory (recall) to testify accurately. The second is a moral question: will a child who is already a victim be further victimized by cross-examination, hours of interrogation, and the stress of the direct confrontation with the accused?

A review of current statutes indicates that within state law there is skepticism about the adequacy of children to testify. Generally, it is up to the judge to determine the child's competency before the trial commences. The judge must consider whether the child can distinguish truth from falsehood, the child's appreciation of the need to tell the truth, and the child's cognitive capacity. Although some judges are trained in child development or are remarkably astute, there is some question as to the value of the judge's determination with very young children. Melton et al. have suggested that children simply be allowed to testify and that the jury be left to determine the child's competency and credibility (5).

CHILD COMPETENCY

Two areas of competency are essential in considering children's testimony: competency in describing the

Presented at the 23rd annual meeting of the American College of Psychiatrists, Marco Island, Fla., February 12–16, 1986. Received March 28, 1986; revised Aug. 21, 1986; accepted Sept. 17, 1986. From the Arizona Health Sciences Center. Address reprint requests to Dr. Yates, Department of Psychiatry Arizona Health Sciences Center, University of Arizona, Tucson, AZ 85724.

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events on the witness stand (cognitive skill) and competency in accurately recalling the alleged crime (memory). Related questions include whether the child can comprehend an attorney's questions or the meaning and purpose of the legal proceedings, whether the child's perception of events will withstand the stress of testifying, whether the child could pay attention to the happenings and remember them for a sufficient length of time, and whether the child can distinguish fact from fantasy. Psychiatrists may be asked to consider these issues in their capacity as consultants to the court.

Competency to Describe the Event

Attorneys and judges are concerned about the consistency and validity of young children's testimony. Several countries, including Israel and Germany, require that only specially trained professionals interview child witnesses (1, 6, unpublished 1982 work of Trankell) because children can be easily influenced by the examiner and the character of the examination. Even after a child has accurately described events during the initial criminal investigation, the child may give contradictory testimony in court in response to either leading questions or misleading information introduced in earlier questions (7, 8). As adults tend to be more suggestible when responding to an authoritative person (9, 10), children may be particularly suggestible when they are asked leading questions by an authoritative adult. Some children are easily intimidated; fortunately, juries are often antagonized by such tactics. In addition, many children seek to please adults and will provide the answer the adult seems to wish. Events that are not personally significant or events that might have occurred but actually did not are especially subject to suggestion.

Children younger than age 6 or 7 have a limited attention span. Therefore, they may not notice all the facets of a detailed inquiry and may not attend at all when kept on the stand for an hour or more. Once their initial attention fades, some children refuse to answer, or they give random, meaningless responses that may be attacked on cross-examination. Well-placed, brief recesses are valuable.

Attorneys who are not trained in child development may ask questions that are too sophisticated or complex, thereby confusing the child. When bewildered, many young children will answer the attorney's questions as best they can without checking out the actual meaning. Sometimes children will say no when they mean yes, especially in response to a double negative. To be understood, questions must be simple, brief, and reasonably concrete. When the interviewer has a preconceived notion of what happened, he or she is not likely to obtain an accurate account from the child (11). In court this is relevant in that attorneys usually do have preconceived notions about the crime and how the child "ought" to respond, creating in effect a strong projective identification. Children are more susceptible than adults to projective identification, since they have not consolidated an identity of their own. What the child "knows" depends on the questions asked (12).

Precautions to Ensure Competency

A few easily expedited precautions would prevent many of the apparent contradictions in children's testimony. If the child first is encouraged to give a narrative report of what occurred, to establish his or her knowledge base, subsequent answers would be more easily understood or redefined. The use of props by the child can greatly facilitate the explanation. The judge may caution attorneys who adopt an overly authoritarian or ingratiating stance and may instruct them to avoid leading questions as far as possible. The judge also can clarify apparent contradictions by speaking directly to the child witness (13).

Competency to Recall the Event

Young children asked to recall materials make more errors of omission than do adults. However, the diminished recall is not due to an intrinsic defect in memory function. The development of strategic skill in organizing memories and in generating visual images to facilitate recall occurs between ages 5 and 10 (14, 15); very young children therefore have not yet acquired this skill. In addition, young children have accumulated less life experience on which to flag memories. If children are asked to recall materials with which they are familiar through everyday experiences, their memories are at least as good as—and may be better than—the memories of adults (16, 17). When children remember a personal, emotionally charged event such as a molestation, differences decrease or disappear and children's recall becomes as accurate as adults' recall (18, 19). Indeed, in some instances children may be less suggestible than adults (7) or may provide details which an adult would have overlooked (20). Sometimes very young children manage to remember interesting items that older children and adults miss completely because older individuals automatically screen out many items as irrelevant (21).

Children can recall events as long as adults can recall them (22, 23), and children as young as age 6 are able to remember a sequence of events accurately (24, 25). In spite of this ability, as time passes children become increasingly reluctant to review disagreeable material (26), indicating the necessity for an expeditious investigation and court appearance. Children age 4–6 years are not able to conceptualize the exact number of times an event occurred or at what hour it took place (27), although they are able to distinguish few from many, night from day, and breakfast time from supper time. An attorney trained in child development could facilitate children's testimony by simplifying time concepts or by hooking them to a familiar event.

Most of the studies on children's ability to recall

events are based on the children's reactions to presentations of pictures, stories, or films. These materials are of variable interest to children and are not the personally significant events that are most subject to recall. It would be essential to study children's recall of naturally occurring, anxiety-provoking events such as the first visit to the dentist's office or the first day at nursery school, that is, real-life experiences which are somewhat traumatic (13). Very young children can remember extremely traumatic events, such as the murder of a parent, with indelible, highly accurate, and detailed visual images (28). One child who was barely 3 when she was kidnapped, sexually abused, dropped into a cess pit, and abandoned repeatedly identified the offender from a series of pictures in spite of attempts to confuse her. Later, the striking accuracy of her report was confirmed through the confession of the man she had accused (29).

Fact or Fantasy?

The court wonders if children can distinguish fact from fantasy, dreams from waking events, or imaginary companions from real persons. Recent research by Johnson and Foley (30) on children age 6 and older indicates that although these children may have difficulty distinguishing their thoughts from their own actions, they are able to distinguish their own thoughts from another's actions in eyewitness situations. However, we still do not know whether children can discriminate their own thoughts about another person's actions from that person's real actions (13). This issue is of extreme importance when an oedipal-age child attributes sexual intent to a parent. A recent case may illustrate:

Case 1. A 40-year-old single-parent father of a 5-year-old boy practiced holistic health by bathing nude in the spa with the child and massaging the child's back, feet, legs, and inguinal lymph nodes. During a custody dispute, the child's mother accused the father of sexual molestation. When questioned by a police investigator, the child indicated that the activities with his father were intended to sexually stimulate both of them, although his description of the activities was exactly the same as the description rendered by his father.

This case raises the issue of whether the child's perception of events is not the most crucial issue; that is, if the child perceives that the father was sexually stimulating him, this would carry the risk of emotional damage and could constitute legal abuse. Inasmuch as most youngsters do have sexual fantasies about parents and tend to perceive commonplace events as sexual, the phenomenon cannot be viewed as pathological or as legal abuse. The fact that these fantasies come to light during the course of a sexual abuse investigation merely indicates that we are now asking children questions that facilitate the verbalization of oedipal fantasy material. Nonetheless, in a case such as this, a careful evaluation is indicated to determine whether there was a confusion of fact and fantasy or actual sexual misuse of the child.

MORAL ISSUES

Children can be helped or harmed through participation in court proceedings, although to date there are no published outcome studies concerning the extent to which children are helped or harmed by testifying and how this might be influenced by the outcome of the trial. In our experience with a number of these youngsters, children who have been helped describe a sense of confirmation that they were correct, trust in the fairness of the legal proceedings, relief from the fear that the accused will get out and punish them, and the working through that occurs with a public revelation. Children who have been hurt by participation cite the confusion and sense of failure attendant upon a "successful" cross-examination, guilt because they participated in the crime but were not punished, guilt over the harm done to a valued family member, terror on confronting the accused, exhaustion after hours of testimony, separation from family members who were not permitted in the courtroom, fear that they will be found guilty and put in jail, fear of the strange courtroom setting, and horror at reliving events through testimony. A common concern of young children is that the accused (who may have threatened to kill them if they tell) will jump on them in the courtroom. Many children who are the victim of incest and accuse their own parent fear that the parent will never forgive them.

Although even very young children have a rudimentary understanding of the legal process, the younger the child, the less knowledge he or she has with which to understand the complexities of the proceedings. Thus, young children are more likely to interpret the proceedings in the light of expectable happenings at home or at school, to wit, one 5-year-old who thought that the judge would jail her as "the bad one" because she could not answer all the questions. Participation in a trial is more likely to be traumatic for the young child witness.

Minimizing the Trauma

The trauma for the young child witness can be lessened in spite of the legal system's disinclination to change. Following Colorado's lead, several states now allow children to be examined in a separate chamber with the judge and opposing counsel while the accused views the proceedings on a video monitor or through a one-way screen. However, the constitutional rights of the accused to have a public trial, to consult his or her attorney, and to confront the accuser may be violated by placing the child and the defense attorney in a separate chamber. This has not yet been fully tested (31). The vast majority of jurisdictions continue to demand the face-to-face confrontation as specified in

the Constitution. Some jurisdictions require videotaped depositions of children in sexual assault cases, which in the future may eliminate the need for the child to appear in court (13). Many individuals who are involved in the tedious and redundant evaluation process would like to see the initial examination of the child conducted by a person trained in child development. The examination would be taped and used in place of the child's testimony should the case go to court. Unfortunately, this humane approach probably cannot be expedited given our legal constraints.

The most expeditious changes would occur through the education of judges. Through the judge's discretionary powers, child witnesses may be seen in chambers, granted recesses, or be accompanied to the courtroom by a familiar supportive adult. The judge may caution attorneys who question children inappropriately and may speak directly to the child. The court may appoint a special attorney with a background in child development to examine the child. This attorney would use questions supplied by the other attorneys and would have the right to object to questions that might confuse or be unduly upsetting to the child (1, 32).

Preschool and grade-school children who must testify could be prepared by visiting the courtroom, by meeting the judge, if possible, and by having the procedures explained in understandable terms. Role playing is helpful for older children. However, serious objections may be raised to any of these interventions because it is conceivable that they might alter the children's attitude or testimony (2).

The Psychiatrist's Role

Psychiatrists are called upon to evaluate the cognitive and emotional aspects of the child's competency to testify; they may also be called upon to treat traumatized children or to advise the court as expert witnesses. In these roles, psychiatrists are not likely to influence the process by which children testify. However, state legislatures may be influenced through a concerted effort by state psychiatric and pediatric societies. Awareness of child testimony issues is increasing within the American Psychiatric Association and the American Academy of Child Psychiatry, whose council has just adopted a policy statement of recommended procedural modifications to protect children who testify (33).

In the case of the 3-year-old girl in Colorado who was molested and abandoned in a cess pit (29), the treating psychiatrist also served as the court examiner, directly questioning the child from behind a one-way screen, while responding to the attorneys' questions through a tiny transmitter in his ear. That this was accomplished at all is a remarkable feat, the constitutionality of which must be tested at the appellate court level. However, if child witnesses are to be humanely treated and protected from further damage, further involvement of child psychiatrists is clearly indicated.

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TSH and Prolactin Responses to TRH in Patients With Premenstrual Syndrome

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The thyroid-stimulating hormone (TSH) and prolactin responses to thyrotropin-releasing hormone (TRH), administered during the follicular and luteal phases of the menstrual cycle, were examined in 14 women with prospectively confirmed premenstrual syndrome and in nine control subjects. There were no differences in basal or maximum increase in TSH or prolactin values between menstrual cycle phases in patients or in control subjects or between patients and control subjects in either phase. However, there was significantly greater variability in TSH response to TRH among symptomatic patients (seven of 10 patients: three with blunted and four with augmented response) than among control subjects (none of nine patients).

(Am J Psychiatry 1987; 144:480–484)

Premenstrual syndrome is a disorder characterized by dramatic changes in mood, behavior, cognition, and somatic functioning in relation to the menstrual cycle. A variety of different syndromes seem to exist (1), characterized by the relative prominence of particular symptom constellations. However, the key defining feature of premenstrual syndrome is the timing of symptoms; i.e., symptoms should appear during the luteal phase of the cycle and remit at or shortly after menstruation (2).

Because many early investigators failed to sufficiently consider the critical temporal component of premenstrual syndrome by prospectively confirming the timing of their subjects' symptoms, the samples in many studies have been heterogeneous and the results confusing and inconclusive (3). No convincing evidence exists to relate cyclic hormonal fluctuations to various premenstrual symptoms. Three recent studies that used careful prospective methods to select subjects failed to find abnormalities in cyclic fluctuations of progesterone and estradiol (4; Rubinow et al., unpublished manuscript) or in basal follicular and luteal phase prolactin levels (5), despite widespread focus on these two systems as potentially etiologic in premenstrual syndrome (2, 6, 7).

There is clearly a need for research strategies other than measurement of basal hormone levels. Since several reports have suggested a relationship between premenstrual syndrome and psychiatric illness, particularly affective disorder (8), an alternative approach would be to search for endocrine abnormalities that have been specifically associated with depression. One study (9) which used this approach found that women with premenstrual syndrome, in contrast to patients

Received Feb. 28, 1986; revised July 2, 1986; accepted Sept. 12, 1986. From the Unit on Peptide Studies, Biological Psychiatry Branch, NIMH, Bethesda, MD. Address reprint requests to Dr. Rubinow, Unit on Peptide Studies, Biological Psychiatry Branch, NIH, Bldg. 10, Rm. 4C-434, 9000 Rockville Pike, Bethesda, MD 20205.

with depression, do not show evidence of cortisol hypersecretion in either the follicular or luteal phase as measured by 24-hour urinary cortisol level and the dexamethasone suppression test (DST). Another strategy would be to examine levels of hormone stimulated by either receptor-specific drugs (e.g., clonidine) or hypothalamic releasing hormones.

To encompass both of these approaches, we administered the thyrotropin-releasing hormone (TRH) stimulation test in the follicular and luteal phases to 14 women with prospectively confirmed premenstrual syndrome and to nine female volunteers. We were interested in the thyroid-stimulating hormone (TSH) response to TRH because depressed patients have shown both reduced (i.e., blunted) (10) and augmented (11) TSH responses to TRH. We also were interested in the prolactin response to TRH because of reports that depressed women show reduced prolactin responses to TRH (12) and because of the possibility that stimulated prolactin levels might be abnormal in women with premenstrual syndrome, even if basal prolactin levels are not (5).

METHOD

The subjects for the study were 14 women suffering from premenstrual syndrome and nine female volunteers. The patients ranged in age from 29 to 49 years (mean±SD, 40±5.0), and the volunteers ranged in age from 22 to 50 years (mean±SD, 31.8±9.5). Although the patients were significantly older ($t=2.77$, $p<.05$), TSH and prolactin responses to TRH are not known to vary with age in women of this age range (13). All patients and control subjects reported regular (no more than 2–3 days variability from cycle to cycle) menstrual cycle lengths, ranging between subjects from 21 to 30 days. The patients were free of current (at intake and at time of testing) or recent (within the past year) psychiatric or medical illness and had the timing of their mood symptoms (either depression or anxiety) prospectively confirmed by twice daily visual analogue self-ratings. As described elsewhere (14), 30% more mood symptoms in the week before menses than in the week after menses in at least two of three cycles was required for entry into the study. To determine if patients were also symptomatic during the months that testing took place, scores on the Beck Depression Inventory and the Spielberger Anxiety Inventory (15) during both the follicular and luteal phases were compared. A 10-point increase from the follicular to the luteal phase was required for a patient to be considered symptomatic. Volunteers had no lifetime personal or family psychiatric history and no recent medical illness; they also had rated (before testing) their moods daily over several menstrual cycles to confirm the absence of any premenstrual mood changes. All patients and volunteers were medication free at the time of the study. However, one patient, before the scheduling of her second TRH test, began to take lithium carbonate for cluster headaches; the results of only her medication-free TRH test were used in the data analysis.

The patients with premenstrual syndrome had their lifetime psychiatric diagnoses and freedom from current psychiatric illness determined by administration of the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) interview (16). Family psychiatric history in first-degree relatives was similarly determined, and a psychiatric diagnosis was made on the basis of the Research Diagnostic Criteria (17) by using a modified SADS-L interview. To identify the type of premenstrual syndrome (1) reported by our patients, we obtained a detailed description of premenstrual phenomenology by a previously described method (18). All 14 women had moderate or severe premenstrual changes in mood and in at least four of seven symptoms associated with a *DSM-III* diagnosis of major depressive disorder; our method allowed assessment of only seven of the eight required symptoms, since loss of interest and loss of capacity for pleasure were combined as a single item. Before the series of TRH stimulation tests, each patient and control subject had a complete clinical chemistry profile, including hematologic and thyroid function indexes, to exclude the presence of any medical illness or thyroid disease.

Each patient and control subject had two TRH tests performed as outpatients in an ambulatory care clinic, one in the follicular phase and one in the luteal phase. The patients and control subjects did not differ with respect to the timing of testing for follicular (20±4.6 and 20±3.5 days, respectively, before menses, $t=0.22$) or luteal phases (4.21±3.5 and 5.1±1.9 days before menses, $t=0.68$). All subjects were instructed to have nothing to eat or drink after midnight and arrived between 8:00 and 9:00 a.m. After the intravenous line was inserted, two basal blood samples were obtained at 15-minute intervals, 500 μg of TRH were given over 1 minute, and blood was drawn at 30 and 45 minutes for measurement of TSH and prolactin levels. The blood was centrifuged, and the plasma was frozen at −60°C until the time of assay. TSH and prolactin levels were determined by radioimmunoassay with intra- and interassay coefficients of variation of 6% and 15% for TSH and 7% and 16% for prolactin. Frozen basal samples also were used to determine T_4 (by radioimmunoassay); a free T_4 index was calculated from the T_4 and T_3 resin uptake. The maximum stimulated values (peak value minus basal value) for each hormone (Δ_{max} TSH and Δ_{max} prolactin) were used for analyses of endocrine response.

Before data analysis, the subjects' anxiety and depression scores were compared between follicular and luteal phases to determine the presence of premenstrual symptoms during the time of testing. No control subjects showed a change greater than 5 on either the Beck or Spielberger (15) scale (mean±SD changes, 0.1±2.2 and 0.5±3.8, respectively), and 10 of 14 premenstrual syndrome women showed at least a

10-point change on one of these scales and substantially greater changes in most cases (mean±SD changes, 13.4±8.4 and 20.6±7.56, respectively; N=10). Although four patients did not have a premenstrual mood change during the month of testing, they had prior and subsequent evidence of premenstrual syndrome and so were included in the analysis. Thus, all comparisons were made with two different patient groups: the 10 symptomatic premenstrual syndrome women versus the nine control subjects and the entire group of 14 premenstrual syndrome women versus the nine controls.

Potential follicular-luteal phase differences in either basal or Δ_{max} values of TSH and prolactin were assessed in both groups by means of a paired t test. Hormone values in patients and control subjects were compared separately for each phase with a group t test. Because of previous reports suggesting that depressed patients have increased variability of pituitary hormonal response to TRH (13), we also determined, for each menstrual cycle phase, whether the variances in the two groups were different, using a one-tailed F test. Finally, we used the Δ_{max} TSH values obtained in our control subjects to establish a normal range for maximum TSH responses to TRH for this assay and these testing conditions. Values for Δ_{max} TSH obtained in these subjects ranged from 8 to 31 μU/ml, which provided a normal range similar to that reported by Sawin et al. (19). Using the range of values obtained in control subjects, we compared the proportion of abnormal values in the two groups by using Fisher's exact test. T_4 and a free T_4 index were correlated with Δ_{max} TSH values for each group by means of a Pearson correlation.

Clinical-endocrine relationships were analyzed in the symptomatic patients by correlating luteal phase depression and anxiety scores with luteal phase Δ_{max} TSH and Δ_{max} prolactin values and by correlating follicular-luteal phase difference scores for depression and anxiety with the corresponding difference scores for Δ_{max} TSH and Δ_{max} prolactin. Finally, the prevalence of personal and familial psychiatric diagnoses was compared in patients with and without abnormal TSH responses to TRH by using Fisher's exact test.

RESULTS

Within patient and control groups, there were no significant follicular-luteal phase differences in basal or Δ_{max} values of either TSH or prolactin (paired t test, df=13 for premenstrual syndrome patients and df=8 for control subjects). Between the patient and control groups, there also were no significant differences in basal or Δ_{max} values of TSH and prolactin for either the follicular or luteal phase (group t test, df=16). However, in both phases, symptomatic patients showed significantly greater response variability in Δ_{max} TSH ($F = 4.87$, df=17, $p<.05$, for the follicular phase; $F=3.22$, df=16, $p<.05$, for the luteal phase). On the basis of a normal range of values from 8 to 31 μIU/ml, Δ_{max} TSH was abnormal in seven of 10 symptomatic patients (11 of 19 TRH tests), and Δ_{max} TSH was normal in all four asymptomatic patients and, by definition, in all control subjects (Fisher's exact test, symptomatic patients versus control subjects, $p<.001$). All T_4 and free T_4 index values at the time of the TRH infusions were within normal limits. For both groups, there were no significant correlations between Δ_{max} TSH and either total T_4 or free T_4 index. We found no significant correlations between endocrine response (Δ_{max} TSH and Δ_{max} prolactin) and depression or anxiety ratings for either the luteal phase or the change from follicular to luteal phase (analyzed only in the symptomatic patients).

Data on the personal and family psychiatric history of each patient as well as their Δ_{max} TSH response to TRH are given in table 1. Ten of 14 patients had a past psychiatric history, and seven of 14 had a family psychiatric history in first-degree relatives. Patients who were asymptomatic at the time of this study were as likely as symptomatic patients to have a positive personal or family psychiatric history. The proportion of patients with a personal psychiatric history (72%) as well as a history of major depression (42%) was identical among patients with abnormal (i.e., augmented or blunted; N=7) and normal (N=7) Δ_{max} TSH response to TRH. A family history of depression appeared significantly more often in patients with normal TSH responses to TRH (Fisher's exact test, $p<.05$).

DISCUSSION

There were no differences in either basal or Δ_{max} TSH or prolactin between menstrual cycle phases in patients or in control subjects, suggesting that there is no state-dependent change in TSH or prolactin associated either with the menstrual cycle or with premenstrual symptoms. This extends prior findings (from dexamethasone suppression test results) of a lack of menstrual cycle phase difference in neuroendocrine tests reported to be abnormal in a state-dependent manner in some depressed patients (9), although it must be emphasized that blunted TSH responses do not always normalize in depressed patients after clinical recovery (20). Our results also replicate previous findings of the absence of menstrual cycle phase-related differences in basal prolactin levels in women with premenstrual symptoms (5) and extend these findings by demonstrating that women with premenstrual symptoms do not show differences in stimulated prolactin levels. However, since peak prolactin responses can occur as early as 15 minutes after TRH in some women (21), our method of taking an initial sample at 30 minutes might have resulted in an underestimation of peak response.

Although we failed to find any patient-control differences in either phase for any of the four endocrine

TABLE 1. Personal and Family Psychiatric History and Δ_{max} TSH Response to TRH During Both Menstrual Cycle Phases for 14 Patients With Premenstrual Syndrome

Patient	Psychiatric History		Δ_{max} TSH (μIU/ml)	
	Personal	Family	Follicular Phase	Luteal Phase
Symptomatic				
1	Major depression	Major depression	34.2[a]	—
2	Generalized anxiety	None	43.1[a]	40.2[a]
3	None	None	44.0[a]	45.2[a]
4	None	None	32.4[a]	32.6[a]
5	Major depression	Substance abuse	4.3[a]	1.4[a]
6	Major depression	None	4.7[a]	8.9
7	Generalized anxiety	None	5.9[a]	20.2
8	Major depression	None	13.0	17.1
9	Bulimia	Major depression	11.6	13.1
10	None	Schizoaffective disorder	17.1	17.2
Asymptomatic[b]				
11	Major depression	None	14.5	14.5
12	Major depression	Major depression	19.8	19.2
13	Panic disorder	Major depression	8.0	7.1
14	None	Major depression	14.0	15.9

[a]Abnormal TSH response to TRH.
[b]Asymptomatic at the time of TRH testing.

measurements, our finding of a significantly higher variance in TSH response in symptomatic patients than in control subjects, along with a high prevalence of abnormal TSH responses, is provocative. These abnormalities were not confined to a particular phase of the cycle and occurred despite normal thyroid hormone levels and normal basal TSH levels.

The majority of our symptomatic patients with abnormal TRH tests (four of seven) showed evidence of subclinical hypothyroidism (i.e., Δ_{max} TSH values greater than 32 μIU/ml), partially replicating the findings of a recent study (22). A previous report has suggested that subclinical hypothyroidism may be particularly associated with rapid-cycling forms of manic-depressive illness (23). More importantly, recent studies (24–25) have documented the presence of subtle postmenstrual mood elevation accompanying the monthly periods of premenstrual depression in premenstrual syndrome patients. These data suggest that premenstrual syndrome may resemble rapid-cycling forms of bipolar illness not just in the frequency of episodes but in the bipolarity of mood changes. At present, the source of these patients' thyroid abnormality is unclear. Recent evidence (26) suggests the utility of obtaining antithyroid antibody titers in future studies to identify autoimmune thyroiditis, a frequent cause of augmented TSH responses to TRH.

One of the remaining six symptomatic patients had a blunted TSH response in both menstrual cycle phases, and two additional women had a blunted response in the follicular phase only. In patients with major depression, the prevalence of blunted TSH responses is approximately 30% (20). While responses normalize in some patients at clinical recovery, abnormal responses persist in others after remission of symptoms, suggesting that the abnormal response may be a trait marker in some patients (20). Although the prevalence of blunted responses in these premenstrual syndrome patients is comparable (i.e., 30%) to that seen in depressed patients, responses in two women were selectively associated with the asymptomatic (follicular) phase, while responses in the third were abnormal in both phases. Thus, in contrast to findings in some depressed patients, blunted TSH responses show no evidence of state dependency in women with premenstrual syndrome. In fact, since two of these three women had a history of major depression, it is possible that their blunted responses represent a trait marker related to those past depressions. This, of course, does not rule out the possibility that the briefer episodes of premenstrual depression may be biologically similar to episodes of major depression, especially since the prevalence of blunting is similar in both groups.

Although our sample size was small, the high variance of TSH response to TRH appeared to be confined to symptomatic women. Since asymptomatic women clearly manifested premenstrual mood changes in previous months and differed from the symptomatic women only in failing to demonstrate premenstrual mood changes during the month of testing, it is possible that they had a less regular, less consistently present premenstrual syndrome. This would suggest, then, that TSH response abnormalities might be confined to, or found more frequently in, women with a regular syndrome that occurs each month and, hence, might constitute a marker for a more severe course of illness. In light of this possibility, future investigators of the neurobiology of premenstrual syndrome might consider selecting only subjects with consistent, monthly occurrence of premenstrual syndrome (i.e., no symptom-free menstrual cycles) to obtain a more homogeneous and perhaps biologically vulnerable sample. Conversely, the presence of an abnormal response to a TRH infusion might identify a subgroup of patients with premenstrual syndrome who have a distinct

course of illness and/or treatment-response characteristics.

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Sex Distribution of *DSM-III* Personality Disorders in Psychiatric Outpatients

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The author determined the sex distribution of 170 outpatients with a DSM-III *diagnosis of personality disorder measured by standardized instruments and compared his findings with* DSM-III *predictions. They confirmed the prediction of more women diagnosed as having histrionic personality disorder and more men diagnosed as having paranoid, compulsive, and antisocial personality disorders. The predicted excess of women diagnosed as having borderline and dependent personality disorders was not confirmed.*

(Am J Psychiatry 1987; 144:485–488)

In some psychiatric diagnoses, there is a striking preponderance of either men or women, when standardized interviewing techniques with specified inclusion and exclusion criteria are used in carefully selected random samples. For example, the epidemiologic catchment area study (1) found an excess of women with major depression and of men with alcohol dependence.

In antisocial personality disorder, one of the two *DSM-III* personality disorders for which there are data, there seems to be a strong preponderance of men (1). The only other *DSM-III* personality disorder for which data are available is borderline personality disorder; for this disorder Kolb and Gunderson, using the Diagnostic Interview for Borderlines, reported an excess of women in their inpatient sample (2), and this general trend was also reported by Kroll et al. in two inpatient studies (3–4) but not in a third (5).

With the exception of antisocial and borderline personality disorders, there are few hard data for the personality disorders. *DSM-III,* although not giving specific figures, estimates whether more men or women are found in a given personality disorder diagnosis, stating that more women are found in the histrionic, borderline, and dependent personality disorders and more men are diagnosed as having paranoid, antisocial, and compulsive personality disorders. *DSM-III* gives no information on sex distribution for schizoid, schizotypal, narcissistic, avoidant, and passive-aggressive disorders.

One difficulty with the *DSM-III* estimates, however, is that although they used specified inclusion and exclusion criteria, standardized measurement instruments were not used except for antisocial and borderline personality disorders. In fact, such instruments have only recently been developed (6, 7). The purpose of this report was to use standardized *DSM-III* personality measurement instruments in a sample of psychiatric outpatients to test the hypotheses about sex ratios proposed by *DSM-III.* To my knowledge, this is the first such attempt.

METHOD

The sample consisted of 170 outpatients. The first group of 82 patients were randomly selected from new intakes to an outpatient psychiatry clinic. Patients were excluded from this group if they had active signs of psychosis, mental retardation, or organic brain syndrome. Within a week of intake, the 82 patients were given the Schedule for Affective Disorders and Schizophrenia (SADS) (8) to determine axis I disorders. To determine axis II disorders, they were given the Structured Interview for DSM-III Personality Disorders (SIDP) (9), Personality Diagnostic Questionnaire (PDQ) (10), and Millon Clinical Multiaxial Inventory (11), all within the first week. The second group, which consisted of 88 outpatients enrolled in a clinical trial, were recruited by advertising to be part of a pharmacologic treatment study for panic disorder. All had to have panic disorder by *DSM-III* criteria and at least one panic attack a week at the time of entry into the study. Patients were excluded who had psychotic symptoms, organic brain syndrome, obsessive-compulsive disorder, or drug or alcohol abuse within the last year. After being free from all study medication for 1 week, they were given the Structured Clinical Interview for DSM-III (SCID) (12) to diagnose axis I disorders and the SIDP, PDQ, and Millon inventory to diagnose axis II disorders. Since the major focus of the study was axis II disorders, the use of different instru-

Received April 14, 1986; revised Aug. 25, 1986; accepted Sept. 17, 1986. From the University of Iowa College of Medicine. Address reprint requests to Dr. Reich, Department of Psychiatry, University of Iowa Hospital and Clinics, 500 Newton Rd., Iowa City, IA 52242.
Supported by NIMH grant MH-41055.
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ments to measure axis I (SADS and SCID) in the two samples was not a major methodologic problem, especially because the two diagnostic systems (*DSM-III* and Research Diagnostic Criteria) have many commonalities.

The SIDP (9, 13), a semistructured, 160-item interview organized into sections relevant to personality styles, scores *DSM-III* axis II criteria, which can then be used to make *DSM-III* axis II diagnoses. Interrater reliabilities (kappas) for joint interview of inpatient samples have been reported as .85 for borderline, .75 for histrionic, .62 for schizotypal, .45 for avoidant, and .90 for dependent personalities (7). The SIDP, as recommended by its developers, was also given to an informant so that both sets of information could be used in the scoring of a personality disorder. The SIDP was scored before the results of the Millon inventory and PDQ were scored. Raters in this study were trained in part by one of the developers of the SIDP.

The PDQ (10) is a true/false, self-report, 152-item instrument that measures all *DSM-III* axis II disorders. Test-retest reliability for psychiatric outpatients at 1 month has yielded kappas of .56 or above for paranoid, schizotypal, antisocial, borderline, avoidant, and compulsive personality disorders (14).

The Millon inventory is a self-report, true/false, 175-item instrument with test-retest reliability at 4–6 weeks ranging from .77 to .85 in a group of psychiatric patients (11, 15). Recent data (7) show a good correlation between Millon's categories and *DSM-III* personality disorder traits as measured by clinicians.

An important question is whether the SIPD, PDQ, and Millon inventory were appropriate for our outpatient sample. Both the PDQ and the Millon inventory were developed for and validated on (at least in part) an outpatient sample and therefore should be reasonably appropriate. Although there are no data on the validity of the SIDP on an outpatient sample, it is an interview rather than a self-report instrument. Presumably, the probing done by an interviewer is an advantage in making a personality disorder diagnosis. However, it seems appropriate to use several measures when none has been determined to be the standard for the field.

Although the purpose of this analysis was to identify *DSM-III* personality disorders and examine the sex ratios, I examined the sex ratios for both patient groups separately to check for group bias due to different axis I disorders. As no major differences were found by group for sex ratios, I report the results for the combined group. Because of evidence for the validity of the *DSM-III* personality disorder clusters (16–18), these were analyzed. (*DSM-III* divides the personality disorders into three clusters: The first cluster includes paranoid, schizoid, and schizotypal personality disorders [the withdrawn or schizoid cluster]; the second cluster includes histrionic, narcissistic, antisocial, and borderline personality disorders [the flamboyant cluster]; and the third cluster includes avoidant, dependent, compulsive, and passive-aggressive personality disorders [the anxious cluster].) Individual personality disorders were analyzed where sufficient numbers were available. All sex distribution comparisons were made to the overall patient group. This was done individually for the SIDP, PDQ, and Millon inventory. Also, because my colleagues and I have some evidence that these measures do not always agree with each other (unpublished data), a more stringent criterion of being positive on two out of three instruments was also used (consensus). All statistical comparisons were done with Fisher's exact test.

RESULTS

Of the total sample, 83 (48.8%), 95 (60.0%), 110 (66.7%), and 74 (45.1%) were positive for some personality disorders on the SIDP, PDQ, Millon inventory, and consensus measure, respectively. (As not all tests were available on all patients, the total number varies slightly.) The mean±SD age of women and men in the combined group was not significantly different (34.0±11.1 years for women and 37.8±10.4 years for men). The mean±SD years of education also did not differ by sex (14.0±2.1 years for women and 14.9±3.2 for men).

For the 88 axis I panic disorder patients, 37 (42%) also had agoraphobia, 21 (23.9%) major depression, 4 (4.5%) social phobia, and 4 (4.5%) dysthymia. Among the other 88 outpatients with axis I diagnoses, 45 (54.9%) had major depression, 12 (14.6%) drug abuse, 10 (12.2%) alcohol abuse, 11 (13.4%) panic disorder, 5 (6.1%) generalized anxiety disorder, 2 (2.4%) obsessive-compulsive disorder, and 3 (3.7%) bipolar affective disorder. (Since these diagnoses are not mutually exclusive, the percents are not additive.)

Table 1 shows the results of sex distribution for *DSM-III* personality disorders and disorder clusters for groups with enough subjects to allow appropriate statistical analysis. The outpatient sample contained 108 women (63.5%); statistical tests were performed against that prevalence as a baseline. That is, the higher the percent is from the baseline of 63.5%, the more likely it is that there will be a significant excess of women with that disorder. To qualify for a consensus diagnosis, the patient had to have the diagnosis on at least two of the three measures (SIDP, PDQ, and Millon inventory).

For the first cluster, there was an excess of men for an individual disorder and for the overall cluster by all three measurement instruments and by consensus measure. Each disorder in the cluster may be contributing to the overall positive cluster effect, because each instrument indicates that one of the disorders in the cluster has a significant excess of men, although the same disorder is not indicated by the different instruments. For the second cluster, two of three instruments and the consensus measure indicate an excess of women with histrionic personality disorder. For the third cluster, the SIDP shows a strong excess of men

TABLE 1. Sex Distribution of 170 Outpatients[a] With *DSM-III* Personality Disorders According to Three Standardized Instruments[b]

DSM-III Personality Disorder	SIDP Total N	SIDP Women N	SIDP Women %	PDQ Total N	PDQ Women N	PDQ Women %	Millon Inventory Total N	Millon Inventory Women N	Millon Inventory Women %	Consensus[c] Total N	Consensus[c] Women N	Consensus[c] Women %
First cluster	13	4	30.8[d]	52	26	50.0[e]	24	7	29.1[f]	8	2	25.0[e]
Paranoid	11	3	27.3[d]	—	—	—	—	—	—	—	—	—
Schizoid	—	—	—	—	—	—	22	7	31.8[f]	—	—	—
Schizotypal	—	—	—	51	25	49.0[d]	—	—	—	—	—	—
Second cluster	39	25	64.1	54	39	72.2	50	36	72.0	33		72.7
Narcissistic	—	—	—	—	—	—	—	—	—	—	—	—
Histrionic	31	20	64.5	35	27	77.1[e]	24	21	87.5[f]	20	17	85.0[e]
Borderline	18	11	61.1	36	26	72.2	21	17	81.0	17	11	64.7
Antisocial												
Third cluster	65	38	58.5	71	42	59.2	94	64	68.1	57	37	64.9
Avoidant	34	21	61.7	23	17	74.0	30	16	53.3	24	14	58.3
Dependent	40	30	75.0	55	38	69.1	59	40	67.8	47	34	72.3
Passive-aggressive	—	—	—	—	—	—	41	30	73.2	—	—	—
Compulsive	19	5	26.3[f]	30	15	50.0	17	12	70.6	10	3	30.0[e]

[a]The study sample contained 108 women (63.5%); statistical tests were performed against that prevalence as a baseline.
[b]Data are included only for those categories which contained enough subjects to allow appropriate statistical analysis.
[c]The patient had to have the diagnosis on at least two of the three instruments.
[d]$p<.02$, Fisher's exact test.
[e]$p<.05$, Fisher's exact test.
[f]$p<.01$, Fisher's exact test.

for compulsive personality disorder; this is reflected, although more weakly, in the consensus measure for compulsive personality disorder.

DISCUSSION

For the first *DSM-III* personality cluster, our findings are consistent with the *DSM-III* predictions. The finding of more men with paranoid disorder was in the predicted direction. Thus far, there have been no findings to dispute our evidence of a preponderance of men in schizoid and schizotypal disorders and in the overall cluster.

In the second cluster, there was no significant sex prevalence for the overall cluster. Although there were too few antisocial personality disorder diagnoses in the total sample to permit an analysis of this category, the substantial prior work by the St. Louis group (19) does not leave much doubt that antisocial personality disorder is male predominated. There were also too few narcissistic personality disorders for analysis. The findings on histrionic personality disorder are consistent with the *DSM-III* prediction that it is a predominantly female disorder. The data on borderline personality disorder did not meet the Diagnostic Interview for Borderlines and *DSM-III* expectations of a significant excess of women. There are several possible reasons for this; the two most likely are different instrumentation and different samples. The diagnostic interview criteria, although different from *DSM-III* criteria, are highly correlated with them, so different instrumentation is probably not the reason. A more likely reason is the difference in the samples studied. For instance, this study sample was composed of outpatients and the diagnostic interview study sample was composed of inpatients. Also, other forms of selection bias could have accounted for sample differences. Although earlier studies (3, 4) found more women than men with these disorders, they may not have adjusted for a baseline predominance of women in their patient samples.

In the third cluster, the *DSM-III* prediction for a male predominance for compulsive personality disorder was confirmed. However, an excess of women in dependent personality disorders was not confirmed, despite fairly good sample sizes for the three instruments. Again, previous estimates may not have taken the underlying excess of women in the psychiatric population into account. No sex differences were found for avoidant personality disorder or for the overall cluster. There were too few passive-aggressive disorder diagnoses to make a determination.

It is interesting to speculate about the sexual differences found. One possible explanation is that familial potentialities are expressed differently in men and women. For histrionic and antisocial personality disorders, there is some evidence for this in the family study of Lillienfeld et al. (20), who suggested a common diathesis for these disorders, i.e., the disorder manifesting itself as antisocial in men and as histrionic in women. It is also possible that societal pressures mold different behaviors into different patterns or that there are sexually mediated help-seeking behaviors which bring more of one sex than the other to clinical attention.

Certain potential biases of this study need acknowledgment. First, the measures were performed on an acutely ill sample, and state depression and state anxiety may affect personality measurement (21). Second, these outpatient samples were less severely ill than inpatient samples, although more ill than com-

munity samples. Finally, axis I disorders may interact to produce different frequencies of axis II disorders; e.g., a sample of alcohol abusers might have different frequencies of personality disorders than one of obsessive-compulsive disorder patients. Such limitations should be kept in mind in interpreting these results.

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An Effect of Pharmacotherapy on the Psychoanalytic Process: Case Report of a Modified Analysis

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A woman who had appeared suitable for psychoanalysis was persistently unable to develop an analyzable transference. Her history, as it unfolded during analysis, suggested a form of atypical depression linked to a neurochemical abnormality, which appeared to be related to her reluctance to take the emotional risk involved in examining transference phenomena. The analysis was modified by a trial of phenelzine. Changes within the analysis and in the patient's private life after the drug trial ended support the hypothesis that her affective vulnerability had inhibited her ability to engage in analysis of transference before the administration of the drug.

(Am J Psychiatry 1987; 144:489–492)

One of the knottier problems confronting psychoanalysis today is clarifying in an open and operational way what makes an analysis work, and for whom. (In this article the terms "psychoanalysis" and "analysis" are used interchangeably. Both refer to the classical Freudian psychoanalytic approach: use of the couch, a frequency of four or five sessions weekly, free association, analytic neutrality, dream work, defense and transference analysis.) Although there have been, over the past 30 years, a number of reports dealing with the characteristics of psychoanalytic patients, their analyzability, and treatment outcome, other issues related to confidentiality and the nature of the analytic process itself pose such immense problems to the construction of a good research design that, as far as we know, there have not yet been any studies which systematically examine the important question of patient selection.

Until such time as a fuller, more accurate, and reliable understanding has developed, if practicing analysts would expand their exchange of views in the literature concerning their own experiences with patient selection and the nature of the process, we could rather quickly acquire an interim body of clinical data to which we might readily refer—an important resource for comparison, criticism, and replication. If, in addition, such exchanges were to include reports of factors associated with negative as well as positive outcomes, the reservoir of data would become even more valuable. Negative outcomes are all too often inappropriately sequestered from useful inspection, like skeletons in the closet, or avoided, like black sheep. Kris (1) observed that the assessment of a patient's analytic potential may be possible only in the course of the analysis, a fact that others (2, 3) have echoed in the intervening years. Heartened by this observation, we should not be so inhibited in our willingness to examine and report on indications that a patient in the course of analysis is not deriving maximum benefit from psychoanalytic treatment alone.

Believing that the articulation of such enigmas would serve as a pragmatic and efficient means of educating members of our profession about these dilemmas, we present the following case report in order to share such clinical observations. It is a report on an analysand who had been found initially suitable for psychoanalysis but who became, as the analysis unfolded, observably unamenable to psychoanalytic intervention alone until a pharmacological intervention was made. The treatment that followed, while conducted in a classical form, included the use of a drug and would therefore be called a modified analysis.

CASE REPORT

Ms. A was a 39-year-old divorced woman whose presenting symptoms included intermittent periods of depression and a persistent inability during the 7 years since her divorce to establish a satisfactory long-term relationship with a man. She regarded the latter as an especially painful reminder of her sense of aloneness. As she said, "Everyone is in pairs but me." Her lack of success in this respect appeared remarkable in view of her motivation for such a relationship, her attractive appearance, engaging manner, social credentials, excellent education, and history of many long-term friendships with both men and women. At the time she came for evaluation, Ms. A was employed by a local university, where for several years she had worked as an administrator. She had begun to find her job "lackluster" and saw herself growing increasingly lackadaisical in it.

Presented at the 139th annual meeting of the American Psychiatric Association, Washington, D.C., May 10–16, 1986. Received Feb. 18, 1986; revised Aug. 18, 1986; accepted Sept. 17, 1986. Dr. Wylie is in private practice. Address reprint requests to Dr. Wylie, 11 Seventh St., N.E., Washington, DC 20002.

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Ms. A's childhood had been spent in the suburban community of a large midwestern city. Her father's business afforded a prosperous standard of living for the family, and her mother ran their fine house in the role of full-time housewife and mother. Ms. A was the eldest of three children; her sister and brother were 2 and 4 years her junior, respectively. She reported that she maintained frequent contact with her mother and had done so since her college days. However, aspects of this closeness appeared to be reactive, masking painfully conflicted feelings that became manifest in the contradiction between Ms. A's account of the respectful cordiality with which she addressed or interacted with her mother and the guiltily disdainful tone she adopted at other times when describing her mother to the analyst. Her earliest memory of this parent was of her mother's anxious preparations for the daily teatime visit of Ms. A's imperious paternal grandmother, who seemed to Ms. A to dominate the household like a dowager queen.

During the evaluation, Ms. A recalled memories of her father (who had died when she was in her late 20s), which, although ambivalent, were primarily characterized by her idealization of him. When she first spoke of him, it was affectionately and possessively, especially with regard to his early pride in her appearance and excellent school performance. However, these feelings were soon interspersed with a sense of bitter disappointment. For example, her nostalgic reminiscence of the excitement she had felt in the otherwise predominantly female household about the ritual of his evening homecoming was quickly followed by a description of the disillusionment she experienced at his later lack of interest in her during her adolescence. Upon inquiry, Ms. A recalled that the change in her father had occurred during a period in her adolescence when he had stopped working in his business for a number of months and had remained closeted and unavailable in the house. No one in the family had discussed this then or since. Although during the evaluation Ms. A found herself wondering whether her father had become seriously depressed (he had never been hospitalized), her speculations did nothing to attenuate her alternating feelings of anger and recrimination at his having "let me down."

During high school, Ms. A proved herself an excellent student, popular with boys and girls and confident of her social skills. She enjoyed great success acting in school plays. However, after she completed an equally profitable first year at college, her life underwent a distinct change. Unable to recall a specific precipitant or even to describe this change in any detail, Ms. A was only able to say that she had "just lost confidence" socially and academically. She perceived herself as increasingly less able and attractive than her collegemates—socially awkward and shy. In her words, "I seemed to miss cues and I seemed always to appear aloof." Nevertheless, through her persistent effort, she continued to be an excellent student and managed to maintain a wide range of activities. Shortly after finishing college she married. While her marriage was considered an "excellent and enviable match" by her family's social criteria, Ms. A's lack of confidence remained unabated.

During the initial interviews, it became clear that Ms. A had struggled for many years with intermittent, noncyclical episodes of depressed mood. During these episodes various of her physicians (at one time, shortly after her marriage, it was a general practitioner; later, during her second pregnancy, her obstetrician; another time, after her divorce, a psychiatrist) had each prescribed amphetamines to relieve her symptoms of fatigue and mood disturbance. In each instance the amphetamines had proved markedly effective, in contrast to a one-time trial of tricyclics, which had been notably unsuccessful, as had a brief period of psychotherapy without medication.

Information garnered in the evaluation (and amplified during her first year of analysis) seemed to indicate that Ms. A's unsuccessful relationships with men fell into one of two categories. There were the initially "good" relationships, which she wondered whether she had somehow played a part in inadvertently undermining, even though during the relationships she had only been aware of feeling that the men were acting in a "particularly painful and thoughtless manner" toward her. For other relationships, it became patently clear to Ms. A, once she became involved, that they were incompatible, unacceptable, and even offensive to her because of fundamental and irreconcilable differences between her own and her partners' life styles and values. In other words, her choices had been poor. During the initial interviews she expressed puzzlement about how, in the first place, she had overlooked these clues that now seemed so "clear."

In both types of relationships, despite the retrospective obviousness of warning signs, Ms. A reported that she was "devastated" when a relationship ended and felt herself to be in a state of crisis, during which she was given to striking her fists brutally and self-injuriously against household objects or, in a passion, to scratching her skin until it bled. She described a tendency to overindulge temporarily in food (as she said, her eating habits were at the mercy, so to speak, of her love life) and occasionally to drink too much. She would subsequently feel depressed and at a loss. She had repeated the pattern so often that by the time she came to analysis, she observed that she was wary of attempting any new relationships with men.

In assessing the suitability of prescribing psychoanalysis for this patient according to the APA diagnostic criteria (4), the analyst noted that Ms. A's history gave indications of persistent intrapsychic conflict together with issues of arrested development that were reflected in her symptoms. There was evidence of oedipal-level conflicts that operated through her unresolved ambivalence toward her mother (whom she both devalued and envied) and her father's memory (which she idealized and resented) and that had led her to a series of failed, masochistically tainted relationships with men. Despite the repetition of her agitated response to each rupture, there was strong evidence in the longevity and consistency of her work relationships and the long-time friendships she had maintained with both men and women to support an impression of intact ego functioning. More importantly, Ms. A's responsiveness to the developmental needs of her children (both of whom were excellent students and well-liked by their peers) suggested that her relationship with her own mother had involved "good enough" (5) early nurturing experiences and that the mobilization of preoedipal issues was regressive rather than fixated. The fact that her children had been able to maintain a good relationship with their father, unsubverted by Ms. A despite the divorce, added to this impression. Her history of successful motherhood combined with a capacity for self-reflection during the evaluative interviews added weight to the analyst's diagnostic sense that the characterological container for her neurotic conflicts was essentially sound. Additionally, it was clear from Ms. A's history that she had an adequate capacity for sublimation and an absence of early trauma; she had also given evidence of object constancy. Furthermore, it was clear from her history that she had received only temporary relief from other forms of psychiatric treatment. All in all, the

analyst decided that she had the ability to establish and maintain a therapeutic relationship and could make use of analysis to complete the unfinished developmental business in her life.

Ms. A began the analysis with enthusiasm and hope. During the first year she was forthcoming and associated freely, in this sense readily engaging in the analytic process. However, she was persistently unable to grasp the specific "as if" characteristics of the psychoanalytic situation. Whenever the analyst brought transference phenomena to her attention, she objected, saying that "this is absurd" and that she could not "imagine such things." Although she became accomplished in observing herself outside the analytic hour, she remained intransigent about adapting the same observing capacity to feelings experienced within the hour. Like a "sector" analysis, as long as the locus of interpretations remained outside the "here and now" of the analytic hour, Ms. A was able to make use of, accept, and talk about transference feelings in displacement. For 18 months she continued to view the analyst as a real object, stating, "I do not want to make a new relationship, any kind of relationship.... I don't want another rejection." In addition to being unable to approach the conflicted and erotized transference issues hidden behind her resistance (which had taken the form of this fear of rejection) and therefore being unable to establish a stable, workable transference configuration, Ms. A was also struggling with recurrent feelings of depression.

The extended duration of Ms. A's reluctance to risk a therapeutic relationship, in combination with three other factors—depressive mood, a history of severe sensitivity to rejection, and a history of self-injurious behaviors (which became clearly illuminated in the first 18 months of the analysis)—brought to mind an article by Liebowitz and Klein (6) on hysteroid dysphoria. Klein had written earlier on the subject:

> The primary defect of hysteroid dysphorics is their affective vulnerability.... These patients have a pathologically heightened emotional reactivity to approval or disapproval, and other aspects of their behavior are expressions of this defect or attempts to compensate for it. (6, p. 558)

> This could be explained by fluctuations of an endogenous amphetamine-like substance whose level is affected by interpersonal stimuli....Using this model, hysteroid dysphorics may be simply suffering from an extreme of such reactivity due to an unstable control mechanism. This in turn could be explained as an inherited or an acquired defect, or as an interaction of both. (6, p. 561)

In their article Liebowitz and Klein presented a form of atypical depression that seemed to fit Ms. A's case: a chronic, nonpsychotic disturbance involving repeated episodes of abruptly depressed mood in response to feeling rejected, a history of temporary abusive reliance on food and alcohol when depressed, inappropriate love objects that are quickly overidealized, self-mutilative acts such as scratching and picking at the skin, a history of having been a performer, a high frequency of affective disorders in first-degree relatives, a history of reliance on dextroamphetamine to maintain mood and energy, and a lack of response to tricyclic antidepressants.

Because Ms. A had, in many respects, developed a good working alliance and remained highly motivated despite her depressive feelings, and because it did not appear that the psychoanalysis alone was effective, modifying the analysis by adding a trial of the drug recommended by Liebowitz and Klein (6) seemed appropriate. The purpose was to reduce her sense of excessive affective vulnerability, which seemed to be interfering with her ability to affectively risk approaching the interpretations of transference issues. It was hypothesized that if this interference were removed, Ms. A would gradually be able to bring her observing self into the treatment hour to experience and analyze the transference—the feelings underlying her depressive episodes—and that she would then be able to work through in the transference neurosis the oedipal-level issues which had originally arrested her developmental processes. Eighteen months after the analysis began, following discussions with Ms. A, a trial of the antidepressant phenelzine, a monoamine oxidase inhibitor, was prescribed by the analyst. All other aspects of the analysis remained unaltered. Over a 2-week period the dose was increased from 30 mg/day to a therapeutic level of 45 mg/day. After 10 months the drug was discontinued.

The first time that Ms. A spontaneously acknowledged the presence of transference feelings within the analytic hour occurred a month after the start of the drug trial. At that time she entered the consultation room and stumbled slightly against the door jamb as she attempted to take a direct look at the analyst. Once on the couch, she opened the hour with the account of a sexually provocative woman in the cast of an opera she had attended the previous evening. This led her to thoughts about the analyst. Without hesitation, she remarked that she found him as attractive as she did the suitable men with whom she had been afraid to seek a relationship. These thoughts were followed by her recollection of a series of memories in which she freely associated to her need to stumble through various past relationships as she had stumbled coming into the office.

From this point on, Ms. A was able to consider the analyst's transference interpretations, first as tentative "possibilities" and then later with occasional humor, as she became actively interested in and curious about the transference phenomenon itself.

An ameliorative effect on Ms. A's sense of affective vulnerability was reported not long after the introduction of the drug, as she described how her general mood had improved. Coincidentally, she reported that she had begun to lose weight, reflecting a fading dependence on food. She found herself becoming more assertive in her work and enjoying what had previously begun to bore her.

During the year that followed the end of the drug trial, Ms. A continued to analyze the aggressive as well as the libidinal components of her transference fantasies and to comprehend their interpretation. This convincingly suggests that prescription of the drug was not an "emotionally corrective experience" (7). Her examination of rescue wishes, dreams, fantasies, and frightening thoughts previously experienced as unintelligible, alien, or unconscious to her were now brought into awareness, successfully analyzed, and perceived as meaningful aspects of herself. Outside the analysis, Ms. A experienced a subtle but clear alteration in her relationship with her mother. This was exemplified by the development of an unambivalent appreciation of the contribution her mother's nurturance had made to her own ability to raise her two children. In a similar way, she gradually integrated her feelings about her father, arriving at a perception of the important influence of his ideals on her dogged efforts to deal

with her own disabling conflicts. A year after the end of the drug trial, Ms. A had developed a solid relationship with a "suitable" man and reported with pleasure on this as it assumed increasing importance for her.

DISCUSSION

Although in 1985 Reiser (8) argued for the efficacy of psychoanalytic interpretation alone in treating a patient's condition that might otherwise have been treated with a psychoactive drug, the patient in the present report did not respond to psychoanalytic interpretation. When Ms. A's depressive mood and sense of vulnerability were eventually conceptualized as part of a constellation of symptoms in a syndrome described by Liebowitz and Klein (6), a specific psychoactive drug was administered. Before, during, and after the administration of the drug, the patient was seen four times a week, and except for use of the drug, the analysis was conducted strictly along classical lines. After the addition of phenelzine, Ms. A became amenable to transference interpretations as well as to the analysis of fantasies associated with taking the drug. This lends support to the hypothesis that her "becoming amenable" was a reflection of the drug's pharmacological effect (i.e., its reduction of the affective vulnerability and alleviation of depressed mood) rather than of the psychological effect of its administration, representing a gratification of her wish to be rescued by an idealized father.

Since a major tool of psychoanalysis is the development of the transference neurosis (the vehicle by which repressed memories can be lifted from the dynamic unconscious), an abnormality in the regulation of the neurotransmitters would compound what under "normal" circumstances is a formidable task. A successful analysis depends on the ability of a patient to withstand the emotional deprivation and the adaptive regression required to permit a flowering of transference. It is an extraordinary process, the sine qua non of which is that the patient is able to undertake this new relationship under the most unusual and stressful of circumstances. Until the administration of phenelzine, Ms. A had been unable to tolerate the sense of affective vulnerability involved in approaching crucial repressed fantasy material. This she had defensively kept out of awareness, unwilling to engage in the study of the transference, which was the only way these fantasies could be made available to her and be worked through. Both her history and her previous response to medication strongly suggested that this patient suffered a disorder of the regulation of her neurotransmitter system characterized by its instability in the face of stress. As Siever and Davis (9) wrote, "Antidepressants, by differentially affecting distinct adrenergic receptor systems, may serve to dampen dysphoric overarousal while enhancing reinforced goal-directed behavior" (p. 1025).

There is little danger that pharmacotherapy will replace psychoanalysis, nor is it likely that chemical factors will be introduced into a classical framework as a matter of course. However, during evaluation and treatment, an adherence to psychoanalytic orthodoxy should not be cause for overlooking pertinent advances in understanding neurochemistry. As Freud (10) predicted, there are avenues to be explored between psychoanalysis and biology.

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Mitral Valve Prolapse and Thyroid Abnormalities in Patients With Panic Attacks

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Panic disorder has been associated with mitral valve prolapse and thyroid abnormalities. Mitral valve prolapse has also been associated with thyroid abnormalities. The authors studied a consecutive series of 65 patients self-referred for evaluation of panic attacks, who were examined for cardiac and thyroid abnormalities. Fifty percent of the patients had mitral valve prolapse according to both cardiac auscultation and echocardiography. Twenty-six percent of the women had some thyroid abnormality; 17% had thyroid microsomal antibodies. There was no apparent relationship between mitral valve prolapse and thyroid abnormalities. These observations suggest that panic attacks, mitral valve prolapse, and autoimmune thyroid disorders are associated.

(Am J Psychiatry 1987; 144:493–496)

Several studies have suggested an association between panic disorder and mitral valve prolapse (1–8). Since many believe that agoraphobia is secondary to panic disorder, the failure to find an increased prevalence of mitral valve prolapse among patients with agoraphobia is puzzling (9–12). An association between thyroid dysfunction and phobic disorders, particularly agoraphobia, has been suggested (13–16). Autoimmune thyroid disorders may also be associated with mitral valve prolapse (17, 18). To date, studies of the relationships among these syndromes have suffered several limitations, including small sample size, retrospective sample selection, and biased sample selection.

We report here the results of a study of a consecutive prospective series of 65 patients with panic attacks who underwent psychiatric, cardiac, and thyroid evaluation.

Presented at the 138th annual meeting of the American Psychiatric Association, Dallas, May 18–24, 1985. Received Dec. 2, 1985; revised July 31, 1986; accepted Oct. 17, 1986. From the Department of Psychiatry and the Department of Medicine, Pritzker School of Medicine. Address reprint requests to Dr. Matuzas, Department of Psychiatry, Pritzker School of Medicine, University of Chicago, 5841 S. Maryland Ave., Chicago, IL 60637.

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METHOD

The sample studied consisted of a consecutive series of 65 patients self-referred for an evaluation of panic attack symptoms. Patients with panic attacks referred by physicians were not included because they often had a previous diagnosis of mitral valve prolapse and were referred because of general knowledge about our interest in this possible association. The mean±SD age of the 65 patients was 36.9±10.9 years; 49 were women and 16 were men; 53 were white, 10 were black, and two were of another racial background. All patients provided consent after the procedures were explained.

All 65 patients participated in an unstructured interview conducted by a psychiatrist experienced in clinical investigation and the use of explicit diagnostic criteria (W.M., E.H.U., or R.M.G.). Diagnosis was by *DSM-III* criteria with the exception that phobias were assessed after panic attacks. Thus, 46 of 65 patients with panic attacks met *DSM-III* criteria for panic disorder. Of these 46 patients, 16 also met criteria for agoraphobia (panic disorder with agoraphobia) and would be classified by *DSM-III* as having agoraphobia with panic attacks. Of the 30 remaining patients meeting criteria for panic disorder, 15 denied any phobic restrictions (uncomplicated panic disorder) and 15 reported limited phobic avoidance but not a general inability to travel alone or enter public places (panic disorder with limited phobia).

Nineteen of the 65 patients did not fulfill the *DSM-III* criteria for panic disorder, either because they never experienced panic attacks frequently enough (N=6) or because they had another disorder that appeared more prominent and persistent than the panic attacks (N=13). Of the 13 patients with another disorder, four had a primary major affective disorder and nine had a primary obsessional disorder. Because these 19 patients did not differ in the variables reported in this study, they will be treated as a single group (panic attacks with another diagnosis).

Twenty of the 65 patients also met criteria for current major depression. In 16 of these patients the major depression was secondary to panic disorder, but in four patients the major depression appeared first and was most prominent. The prevalence of major depression did not vary according to the diagnostic

TABLE 1. Psychiatric Diagnosis and Mitral Valve Prolapse Findings From Echocardiography and Auscultation for 48 Patients With Panic Attacks

	Mitral Valve Prolapse Findings From Echocardiography and Auscultation					
	Both Positive		One Positive		Both Negative	
Psychiatric Diagnosis	N	%	N	%	N	%
Uncomplicated panic disorder (N=13)	5	38	6	46	2	15
Panic disorder with limited phobia (N=12)	6	50	2	17	4	33
Panic disorder with agoraphobia (N=10)	5	50	5	50	0	0
Panic attacks with another diagnosis (N=13)	8	62	1	8	4	31

subcategories except that all the primary depressions were in the group of patients with panic attacks and another diagnosis.

Cardiac Evaluation

All patients were referred for M-mode and two-dimensional echocardiographic evaluation. All recordings were reviewed by at least two readers who arrived at a consensus diagnosis of mitral valve prolapse. The echocardiographic diagnostic criterion was a posterior excursion of 2 mm or more of one or both leaflets during systole on M-mode examination (19) or a backward displacement of one or both mitral valve leaflets beyond an imaginary line drawn across the atrioventricular ring during systole on two-dimensional examination (20).

Of the 65 patients with psychiatric and echocardiographic evaluations, 48 were also seen for a full physical evaluation by a cardiologist (J.A.) interested in mitral valve prolapse and a fellow in cardiology working with him. These cardiologists assessed the presence or absence of a nonejection click with or without a late systolic murmur and the effect of position on the timing of the click. They made a diagnosis of mitral valve prolapse on the basis of typical auscultatory observations regardless of the echocardiographic results that were available to them for review. If the cardiologists disagreed or ascertained the presence of a nonejection click that did not move with changes in position, they made a diagnosis of possible mitral valve prolapse. All other patients were given a diagnosis of no mitral valve prolapse.

Thyroid Function Studies

Fifty-five of the 65 patients underwent thyroid evaluation that assessed T_3, T_4, FT_4I, thyrotropin (TSH), and microsomal and thyroglobulin antibodies. Patients were also asked about any history of diagnosis or treatment for a thyroid disorder. When available, past medical records were reviewed.

RESULTS

The various subgroups of patients with panic attacks (uncomplicated panic disorder, panic disorder with limited phobia, panic disorder with agoraphobia, and panic attacks with another diagnosis) did not differ in terms of age, sex, or duration of illness. Thirty-seven (57%) of the 65 patients referred for echocardiographic evaluation had mitral valve prolapse. The prevalence of mitral valve prolapse within this group showed very little variation by subcategory, ranging from 53% (N=8) among patients diagnosed with panic disorder with limited phobia to 60% (N=9) among patients diagnosed with uncomplicated panic disorder.

Of 48 patients referred for cardiac evaluation, 30 (62.5%) had mitral valve prolapse, seven (14.5%) had possible mitral valve prolapse, and 11 (23%) had no mitral valve prolapse. Differences between groups were not great except that no patient with panic disorder with agoraphobia received a diagnosis of no mitral valve prolapse, compared with 23% to 33% of the other groups. Of the 48 patients evaluated by both echocardiography and auscultation, 24 (50%) met criteria for mitral valve prolapse according to both methods, 10 (21%) were completely free of mitral valve prolapse according to both methods, and 14 (29%) were discordant for the diagnosis of mitral valve prolapse. The psychiatric diagnoses and combined cardiac findings of these 48 patients are presented in table 1.

Thyroid abnormalities were noted in 11 (26%) of 42 women and one (8%) of 13 men. The most frequent abnormality was the presence of microsomal antibodies in seven women (titers=1/80, 1/320, 1/1280, 1/5120 [three patients], and 1/20480), four of whom also had thyroglobulin antibodies (titers=1/40, 1/160 [2 patients], and 1/2500). The next most frequent abnormality was an elevation in T_3, T_4, or FT_4I, which occurred in four patients. Three patients reported a history of thyroid illness and treatment: one patient had had a thyroidectomy for cold nodules, one patient had persistent thyromegaly and episodically elevated T_3, T_4, or FT_4I but no antibodies, and one patient had a history of treatment with thyroid hormone for "thyroid disease."

The prevalence of thyroid abnormalities was not related to the four psychiatric subdiagnoses used in this study or to the presence of mitral valve prolapse. Of 12 patients with a thyroid abnormality, one had a primary depression and two had a secondary depression.

DISCUSSION

This study showed that 50% of patients with panic attacks evaluated by both auscultation and echocardiography had mitral valve prolapse according to both methods. The prevalence of mitral valve prolapse documented by each method alone was somewhat higher: 57% were diagnosed by echocardiography and 62% by auscultation. The prevalence of mitral valve prolapse observed in this clinical series is substantially greater than the 5%–7% prevalence estimated in the general population.

To date, to our knowledge, 14 reports have presented estimates of mitral valve prolapse in groups of psychiatric patients. In eight reports, patients with current panic attacks and diagnoses of panic attacks (1), panic disorder (3, 4, 7, 8), or agoraphobia with panic (5, 6, 11) were examined for mitral valve prolapse. In seven of these reports, mitral valve prolapse was present in 30% to 47% of the patients according to echocardiography, in 25% to 48% of the patients according to auscultation, and in 24% to 40% of the patients according to both. In the eighth report, the prevalence of mitral valve prolapse was only 8%, but the authors (11) indicated that their criteria for the diagnosis of mitral valve prolapse may have been more stringent than those of other groups. In another six studies, selection criteria were not based on current panic attacks and diagnoses included agoraphobia with panic (2, 10), agoraphobia (9), anxiety (12), chronic anxiety (21), and neurocirculatory asthenia (22). The observed prevalence of mitral valve prolapse was low and probably not different from that in the general population, except in one study (2), in which selection criteria included palpitations as well as agoraphobia.

Our results are consistent with the majority of studies that, like ours, chose patients with spontaneous panic attacks whether or not they also had panic disorder or agoraphobia. These results suggest that the prevalence of mitral valve prolapse in such patients is greater than that in "normal" populations. It is important to emphasize that, in the current study, the presence of mitral valve prolapse was determined by both routine clinical and echocardiographic examination. Criteria were defined and applied in each case, although blind diagnostic methods were not used. Such efforts might have reduced the observed prevalence of mitral valve prolapse.

Another finding of this study is that a high proportion of the women (26%) had a thyroid abnormality discovered by history or current examination. Interestingly, there did not appear to be an association between thyroid abnormalities and mitral valve prolapse in this sample.

The most frequent abnormality was the presence of thyroid antibodies. Unfortunately, this sample was small and there was no control group. However, epidemiologic studies of thyroid antibodies (23–27) indicate that prevalence varies dramatically with sex and age. Among women 30 to 40 years old in the general population, estimates of prevalence range from 5% to 13.8%, whereas 25% (N=20) of the women in the same age group in this sample had thyroid antibodies. Thus, in comparison with studies of samples randomly selected from the general population, the prevalence of thyroid antibodies does appear elevated in patients with panic attacks.

The possibility of a high prevalence of thyroid antibodies in patients with panic attacks is of interest in another context. Nemeroff et al. (28) observed that eight (15%) of 53 patients with depression had thyroid microsomal antibodies, although titers were considerably lower than those in the present study. Our results document that the presence of thyroid antibodies is not specific to depression, particularly since there was no association between depression and the presence of thyroid antibodies in our series. However, given the results of Leckman et al. (29), who found that a high proportion of depressed patients have panic attacks, the possibility remains that the presence of thyroid antibodies in depressed patients is specifically associated with panic attacks.

Although our results and others suggest that a relationship exists between panic disorder, mitral valve prolapse, and thyroid abnormalities, the nature of this association remains unclear. All exist independently in many patients, so that a direct causal relationship seems unlikely. Another possibility, however, is that these syndromes share a common etiology. We speculate, with others, that a systemic disorder exists that has a variety of manifestations, including panic attacks, mitral valve prolapse, and autoimmune thyroid disorders. These various manifestations do not appear in any consistent combination but, instead, can appear alone or in any number of combinations, like the symptoms in most syndromes. We further speculate that it is this variability in overt occurrence which accounts for some of the discrepant results reported in studies of mitral valve prolapse and panic disorder. This last model for association opens several lines of investigation. In the end, perhaps the only method capable of settling the issue would be a broadly based epidemiological survey using rigorous random sampling in which the various potentially linked phenomena are studied simultaneously. In this manner, an unbiased estimate of the possible association between panic attacks, cardiac status, and thyroid function might be obtained.

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Indochinese Versions of the Hopkins Symptom Checklist-25: A Screening Instrument for the Psychiatric Care of Refugees

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The United States is accepting the largest number of displaced persons since World War II. Over 70% are Southeast Asians; many have suffered serious war trauma and torture. Cultural differences in health-seeking behavior and lack of specialized mental health services make the recognition of psychiatric distress in Southeast Asian refugees difficult for American health care providers. The authors describe the development and validation of Cambodian, Laotian, and Vietnamese versions of the Hopkins Symptom Checklist-25. This brief, simple, and reliable instrument is well received by refugee patients, offers an effective screening method for the psychiatric symptoms of anxiety and depression, and is especially helpful for evaluating trauma victims.
(Am J Psychiatry 1987; 144:497–500)

Many refugees have serious mental health problems associated with the refugee experience. The office of the United Nations High Commissioner for Refugees estimates that there are currently 15–20 million refugees throughout the world. The United States is accepting the largest number of displaced persons since World War II (1). However, in spite of the often catastrophic experiences of the Southeast Asian refugees (e.g., the Pol Pot genocide in Cambodia) and their high risk for developing serious psychiatric disorders, psychiatric services are extremely limited. In 1983 the U.S. Office of Refugee Resettlement awarded grants for a number of national demonstration projects to redress the lack of mental health care for refugees. The development of three Indochinese versions of the Hopkins Symptom Checklist-25 (Cambodian, Laotian, and Vietnamese) was carried out by one of the national projects at the Indochinese Psychiatry Clinic in Brighton, Mass. (2). The goal was to facilitate the evaluation and treatment of Southeast Asian patients within traditional American medical and psychiatric settings. In this report we present a general overview of the validation and development of the three Indochinese versions of the Hopkins Symptom Checklist-25.

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Funded by the U.S. Office of Refugee Resettlement.

The authors thank Binh Tu and Ter Yang for their advice; Russell Jalbert and Dr. William Anderson for their support; Allene Grognet for transliteration; and Drs. Ronald M. Wintrob, Jane Murphy, and Karl Rickels for consultation on the validity and reliability of this study.

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BACKGROUND

Detecting Psychiatric Problems in Indochinese Refugees

Researchers (3–5) have noted that many patients with psychiatric illness first present themselves to outpatient medical settings. Asians and Southeast Asian refugees virtually always conform to this pattern. The psychiatric problems of primary care patients also are often overlooked by physicians unfamiliar with mental health diagnosis and the symptoms of psychiatric disorder (6). The difficulties in detecting psychiatric problems in Southeast Asian populations in primary care and mental health settings are even more severe (7). The Indochinese refugee patient presents a special challenge to the health care provider. Aside from obvious language differences and the inherent difficulties of interpretation, problems arise from cultural differences as well. These include the tendency of Southeast Asians to feel that medical symptoms are the only legitimate reason to seek help, their general acceptance of folk healers and community resources (such as family, Buddhist monks, Catholic priests) for solving emotional problems, and the widespread lack of familiarity with mental health practitioners and psychiatric institutions in their native countries, particularly in Laos and Cambodia. For the new refugee, mental health problems present an even greater threat because the admission of mental illness marks one as

weak or unable to function. Kinsie (8) and Yamamoto (9) noted that Asians are more likely than Westerners to see mental affliction as a source of humiliation and potential ridicule. Therefore, secretiveness about sharing emotional upset is the prevailing standard. Furthermore, those who have been raped or involved in war trauma may be reluctant to discuss trauma-related events or symptoms with a health care practitioner because they raise painful feelings that the patients often would rather put behind them.

History of the Hopkins Symptom Checklist

The Hopkins Symptom Checklist (HSCL) (10–16) is a well-known and widely used screening instrument that dates from the 1950s. It was originally designed by Parloff, Kelman, and Frank at Johns Hopkins University as a self-report symptom inventory to be used for measuring change in the clinical status of psychotherapy patients (3, 10). In recent years Karl Rickels, one of the HSCL's original developers, and his colleagues have demonstrated the usefulness of a 25-item version of the HSCL (HSCL-25) in family practice (11) and family planning (12) settings. In the family practice study (11) there was a high concordance (86.7%) between the case assessment by the family physician and the patients' own ratings of distress on the HSCL-25.

The HSCL-25 uses 10 items from the HSCL-58 anxiety cluster (being suddenly scared for no reason; feeling fearful; faintness, dizziness, or weakness; nervousness or shakiness inside; heart pounding or racing; trembling; feeling tense or keyed up; headaches; spells of terror or panic; feeling restless, not being able to sit still) and 13 items from the depression cluster (feeling low in energy, slowed down; blaming oneself for things; crying easily; loss of sexual interest or pleasure; feeling lonely; feeling hopeless about the future; feeling blue; thoughts of ending one's life; feeling trapped or caught; worrying too much about things; feeling no interest in things; feeling everything is an effort; feelings of worthlessness). It also includes two additional somatic symptoms (poor appetite; difficulty falling asleep or staying asleep). The scale includes four categories of response ("not at all," "a little," "quite a bit," "extremely"), in keeping with its primary use as a measure of improvement (11).

DEVELOPMENT OF THE HSCL-25 INDOCHINESE VERSIONS

The many American versions of the HSCL have been proven through extensive research to be highly valid and reliable screening instruments (13–16).

Translation of the Instrument

For the Indochinese versions of the HSCL-25, we established semantic equivalence in accordance with the unpublished guidelines of M. Gaviria et al., which are generally accepted in the field of cross-cultural instrument development (17, 18). Gaviria et al. note that "the development of equivalent measures of the same instrument in several languages requires more than mechanical translation; it requires similarity in regards to style and connotation." They stressed the importance of collaboration between indigenous professionals and American researchers through such means as expert panels, "back-translation," and establishment of methods for resolving differences.

Our procedure began with the translation of the HSCL-25 from English into Cambodian, Laotian, and Vietnamese by three experienced Indochinese mental health clinicians fluent in English (members of the Indochinese Psychiatry Clinic staff). These versions were then back-translated blind into English by three bilingual Indochinese experts in the community who were knowledgeable about mental health concepts. Discrepancies were discussed and resolved by each pair of translators. The resulting versions were used in the clinic for 1 year.

In the final preparation of each Indochinese-language version, we consulted several cultural experts who combined native fluency and a knowledge of mental health issues. This group always included a nationally recognized authority and a minimum of six other cultural specialists. In this stage special attention was paid to nuance, idiom, and connotation; phrases translated so literally as to be confusing were replaced by more idiomatic phrases. The suggestions and alterations were then discussed by the three clinic staff members and us. The final version incorporated a number of the suggested word changes and maintained the terminology that had proven over the trial year to be most understandable to the patient population.

Validation of the Instrument

Validation included the three translated Indochinese versions of the HSCL-25 because there was not a large enough sample for each language group alone. Validation was accomplished by measuring the degree of sensitivity and specificity of the HSCL-25 through comparing the HSCL-25 scores with the *DSM-III* diagnoses given by a psychiatrist blind to the HSCL-25 results. This was conducted in the following way. All patients newly admitted to the clinic over 18 months who were not receiving psychiatric treatment or medication at the time of admission (N=65) were given the HSCL-25. First, scores on the HSCL-25 were determined for three categories: total, depression, and anxiety. The total score is the sum of all the scores of the items answered divided by the number of items answered (usually 25); the anxiety score equals the sum of the first 10 item scores divided by 10; the depression score equals the sum of items 11–25 divided by 15. Indochinese patients with depression scores higher than 1.75 were classified as having a clinical depression; Indochinese patients with scores higher than 1.75

on the total score, anxiety score, or depression score were classified as having significant emotional distress. The cutoff point of 1.75 was chosen for its consistency with data obtained from a random general population sample in California (12, 13) (but since there are no community studies using the HSCL in Indochinese communities, it is unknown whether 1.75 is the best cutoff point for this population).

Second, *DSM-III* diagnoses were determined for the new patients through a series of clinical interviews (usually three or more) by an American psychiatrist who did not speak any Indochinese language but was highly experienced with Indochinese psychiatric patients and well-versed in *DSM-III* criteria. This psychiatrist (R.F.M.) was unaware of the patient's HSCL-25 scores. Comparisons were then made between the HSCL-25 scores and the *DSM-III* diagnoses to determine the HSCL's sensitivity and specificity.

The sensitivity of a screening instrument is a measure of the proportion of people with the illness who are correctly identified by the instrument as having the illness. The specificity of a screening instrument is a measure of the proportion of those who do not have the illness who are correctly identified as not having the illness. In our study of the newly admitted patients, the sensitivity and specificity for the presence of depression (based on a score higher than 1.75 on the 15 HSCL-25 depression items) according to the *DSM-III* diagnoses of major depression were 0.88 and 0.73, respectively. These findings are consistent with previous validations of the HSCL (3, 11, 12).

In addition, in a 6-month clinic outcome study, patients were asked to rate the relative success of their treatment. There was a high correlation between the patients' self-assessments of clinical improvement and the changes in their HSCL-25 scores (19, 20). For example, the patients who indicated the greatest improvement also had the lowest symptom levels after 6 months of treatment. In a study of improvement among anxious outpatients, Rickels et al. (20) demonstrated similar findings.

The HSCL-25 translations were also assessed for test-retest and interrater reliability. Test-retest reliability is a measure of the stability of scores across time. These coefficients were determined for 30 patients (10 from each language group). The test-retest coefficients for the three language groups combined were 0.89 for the total score and 0.82 for anxiety and depression; the results for each language group separately were comparable. These findings are consistent with other test-retest evaluations of the HSCL (3). The interrater reliability for the total, anxiety, and depression scores for each of the three language groups was higher than 0.98.

DISCUSSION

The HSCL-25 has several advantages as a screening instrument for Indochinese refugees and is extremely helpful in the clinical setting. The questionnaire is brief and simple in its language and may be self-administered by literate patients. It can be understood by people of all levels of educational attainment. While the HSCL does not supply a diagnosis, it allows the clinician to recognize symptoms universally associated with anxiety and depression (18). The four categories of response, ranging from "not at all" to "extremely," provide a safeguard against simple "yes" and "no" answers, as does the fact that the items are neither questions nor true-false statements. This structure is helpful in determining the severity of a psychiatric disorder and in documenting change in the patient's condition.

The clinicians at the Indochinese Psychiatry Clinic have also found the HSCL-25 helpful in evaluating victims of trauma. This was especially important for Cambodian patients, most of whom had experienced serious multiple traumas under the Pol Pot regime and during their escape into Thailand. These traumas included torture, rape, deprivation of food and shelter, and the witnessing of killings, usually of one or more family members. The clinic staff found that other screening instruments were so comprehensive and/or emotionally intrusive as to be capable of triggering flashbacks and intense emotional reactions. In contrast, the HSCL-25 is a short, nonprovocative instrument that puts words *around* the patient's feelings. Many refugees (especially the trauma victims) are so overwhelmed by their emotions and/or are so shy and reticent that they are unable to articulate their major psychiatric symptoms to interviewers during mental status examinations. The HSCL-25, however, was able to move beyond "just not feeling right" to specify emotional complaints necessary for diagnosis and treatment. The HSCL-25 also seems to be readily accepted by refugee patients because it resembles a medical test. Finally, the use of the HSCL-25 is easily understood by Indochinese paraprofessionals. In a professionally supervised context it allows them to retrieve information about psychiatric symptoms that they generally regard as restricted to the domain of medical professionals.

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The Manfred S. Guttmacher Award

The American Psychiatric Association and the American Academy of Psychiatry and the Law invite applications for the annual Manfred S. Guttmacher Award. The award is given for an outstanding contribution to the literature of forensic psychiatry in the form of a book, monograph, paper, or any other work submitted to or presented at any professional meeting or published between May 1, 1986, and April 30, 1987. The award will be formally presented in May 1988 at the American Academy of Psychiatry and the Law meeting held in conjunction with the annual meeting of the American Psychiatric Association in Montreal, Canada. The recipient is expected to give an award lecture. An honorarium of $500 is provided, and the award will be acknowledged in the APA Convocation program. A nonmember winner's travel expenses will be reimbursed up to $500.

Anyone wishing to apply should submit six copies of the work, along with six copies of an abstract, to Robert L. Stubblefield, M.D., Chairman, Guttmacher Award Board, American Psychiatric Association, 1400 K Street, N.W., Washington, D.C. 20005.

Entries must be received by May 1, 1987. Entries will be acknowledged but not returned.

Applicants' Choice of a Residency Training Program

William H. Sledge, M.D., Philip J. Leaf, Ph.D., and Michael H. Sacks, M.D.

The authors present results from a survey of senior medical students in the class of 1981 concerning their selection of residency training programs in psychiatry. Generally, students were more influenced by clinical training opportunities and quality of life factors and not much influenced by the philosophy of the program. The implications of the findings are discussed from the perspectives of both advising and recruiting medical students.

(Am J Psychiatry 1987; 144:501–503)

Recruitment and selection of qualified medical school graduates continues to be a major concern for psychiatry in general and for residency training directors in particular. Good residents are the backbone of a good training program and are important participants in the life of a department; they have a decisive influence on the quality of the professional life of teachers and attending physicians. As service providers, they more than compensate for their lack in skill and experience with energy and commitment. They do difficult work in difficult settings. A program's residents frequently become a program's faculty. It is important for a department to have the best residents it can possibly recruit. Furthermore, the psychiatric resident represents the future of the profession.

Although the number of American medical graduates going into psychiatry has risen steadily over the last 5 years, the number of available positions continues to exceed the number of American medical graduates who select PGY-1 positions in psychiatry. In 1985 there were 916 PGY-1 positions offered through the National Residency Matching Plan (NRMP), with only 610 filled by American medical graduates (personal communication from NRMP). Even when one takes into account that many students enter psychiatry outside the NRMP, many resident training programs are not filling their available positions. In a situation such as this, where there are more positions than applicants, the competition for desirable students is keen.

Several investigators have studied issues involving medical student interest in psychiatry and the decision to enter the profession (1–6). However, there have been few studies of applicants' perceptions of psychiatric training programs. Sacks et al. (7) studied the experience of a group of applicants at one program, and their investigation revealed that the applicants viewed the interviews with faculty as very important. If the applicants viewed the interviews as too probing or intrusive, they were likely to see the entire visit as negative.

In the present study we examine the perceptions of and criteria used by students in the class of 1981 in selecting a psychiatric residency.

METHOD

To identify medical students entering psychiatric training programs, we obtained a list through the NRMP of all the senior American medical students of the class of 1981 who matched to a PGY-1 position in a 4-year psychiatry program. In the spring of 1981 after the NRMP match results were announced and before graduation, we sent a four-page questionnaire to all 504 senior medical students in American schools who had matched to PGY-1 positions in psychiatry. We followed up our first request with a second mailing in the summer of 1981. Nine questionnaires were returned as undeliverable; 318 questionnaires were completed and returned for a participation rate of 64.2% (318 of 495).

Our response sample was representative of the larger group of senior medical students in the class of 1981. There was no difference between our survey responses and the Association of American Medical Colleges survey responses of 96% of the senior class along the dimensions of race, marital status, and degree program (8). There were statistically significant differences among gender and age categories, with our respondent group comprising more women (35% [111 of 318] vs. 25% [2,643 of 10,631]; $\chi^2=16.75$, df=2, $p<.0001$) and older individuals (35% [111 of 318] vs. 19% [2,016 of 10,610] 29 years or older; $\chi^2=72.73$, df=6, $p<.00001$). The gender differences reflect the greater tendency of women, in comparison with men,

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TABLE 1. Applicants' Rankings of Items for Importance in Choosing a Residency Training Program

Item	Highest Four Rankings		Lowest Four Rankings		Not Ranking		Total
	N	%	N	%	N	%	N
Geography	192	63.8	33	11.0	76	25.2	301
Clinical training	183	61.8	2	0.7	111	37.5	296
Impression made by faculty	145	51.1	7	2.5	132	46.5	284
Intuitive feeling about program	141	47.5	40	13.5	116	39.1	297
Spouse opportunity	103	34.4	100	33.4	96	32.1	299
Impression made by residents	94	32.5	27	9.3	168	58.1	289
Perspective relative to psychodynamic psychiatry	88	30.4	59	20.4	142	49.1	289
Internship	87	29.7	75	25.6	131	44.7	293
Patient population	56	19.8	54	19.1	173	61.1	283
Perspective relative to biological psychiatry	56	19.2	77	26.4	159	54.5	292
Advice from mentor	44	14.5	144	47.5	115	38.0	303
Job opportunities after residency	41	13.9	148	50.3	105	35.7	294
Research training	39	13.2	148	50.0	109	36.8	296
Size	32	11.1	132	46.0	123	42.9	287
Perspective relative to social and community psychiatry	28	9.6	108	36.9	157	53.6	293

to choose psychiatry (2). The age findings may represent differences between those who choose psychiatry and those who choose other medical specialties, although these differences have not been noted in previous studies (1–3, 9).

The respondents to our survey were from 103 medical schools out of a potential pool of 113 American medical schools that had senior students matching to PGY-1 positions through the NRMP; 45% of the schools had one or two respondents, 45% had three to five respondents, and 10% had more than five students responding. The students matched to 102 different residencies (160 programs offered 944 positions through the NRMP; 115 matched one or more students); 49% of the anticipated residencies had one or two respondents, 39% had three to five respondents, and 12% of the programs had more than five respondents.

RESULTS

Applicants were asked to evaluate the importance of 15 qualities of residency training programs in how the qualities influenced their first choice of a program. Applicants were asked to indicate the four most important and four least important factors on the list. These items included the content or orientation of the program and the people associated with it as well as nonprogrammatic factors having to do with the program's setting (i.e., geography and perceived opportunities not related directly to the residency program). Table 1 presents the results of the applicants' evaluations.

Students most often ranked geography as one of the four most important factors. Clinical training available (61.8%), impression made by the faculty (51.1%), and the student's intuitive feeling about the program (47.5%) were the second, third, and fourth most frequently listed factors in selecting a particular training program.

Students also indicated the four least important factors in making their first choice for a psychiatry program. Research opportunities (50%), jobs after residency (50%), and size of the program (46%) were the factors most frequently chosen as being unimportant. Clinical training and impression made by the faculty were rarely indicated to be unimportant (1% and 2.5%, respectively).

Jobs available after residency and research opportunities were not particularly important in the decision making of most applicants, nor were the paradigm orientations of the departments along the dimensions of biological and social/cultural psychiatry. Among these paradigm aspects of the training picture, the psychodynamic perspective was valued most (30.4% of the respondents ranked it in the most important group).

DISCUSSION

The results of this survey are important to the profession and to training program directors; the results also raise some new questions. The response on the geography item is an example of such a question. We envision two different kinds of explanations for the prominence of this item in the rankings of importance. The explanation we favor is based on the fact that when the number of training positions significantly exceeds the number of applicants, most applicants can select from among several programs. In this situation, quality-of-life issues (e.g., geography) may emerge to play a determining role in the choice of a program because high-quality clinical training is available in several different programs. Once several acceptable alternatives are identified, residency applicants may then elevate nonprogrammatic features and base the final decision on these factors.

However, another explanation must be considered. The importance of geography may actually indicate that programmatic aspects of the residency are given

less consideration because programs are not easily differentiated by applicants or because life-style factors are becoming more important in an uncertain economic environment. This explanation has possibly worrisome implications and warrants further investigation.

This study raises questions about the applicants' decision making and suggests that this process may not be based on program features. If the applicant feels unable to differentiate meaningful aspects of the program, he or she may feel compelled to rely on intuition. Decision making that entails the use of intuition after reducing the number of potential choices based on the qualities of the program should not be considered faulty. However, the low ranking of advice from mentor suggests that many students may not have valued advisers who can help them differentiate what is important in choosing a program. On the other hand, it may be that advice from others helps frame the questions, so the candidates themselves are capable of evaluating the criteria.

The relative unimportance of the paradigm perspectives in the choice of a training program also requires additional attention. It could be that what now appeals to applicants is what has been called "eclecticism." Weissman and Bashook's study (9) of the class of 1982 revealed that 60% of students going into psychiatry rated the eclectic philosophy of a program as an important feature.

In understanding these data, another feature must be kept in mind. This is, after all, a survey of only one graduating class and one that marked the lowest point in the recent recruiting of American-educated senior medical students. Since the class of 1981, there has been a gradual increase in the number of American medical students who have decided to go into psychiatry. The class of 1981 is a transition group and thereby might be unusual and different in some significant fashion from preceding or succeeding classes. Furthermore, as many as 20%–25% of the resident class entered a psychiatric residency outside of the NRMP (personal communication with NRMP), and it is also important to examine these future members of the profession.

CONCLUSIONS

Educational programs need to explore their local advisory systems and perhaps more systematically educate medical students about what to consider when deciding on a residency. Given the rapidly changing nature of the profession, it is important that the applicants be provided with realistic expectations about both their training and their future activities. Training directors can enhance their own recruiting positions by attending to quality-of-life matters as well as the programmatic items of curriculum and training experiences.

The health care system is undergoing a substantial transformation. The profession needs to better understand and monitor the factors affecting the entrance into the profession in order to be better prepared to meet the challenges ahead. A study of a more recent graduating class that also compares house staff going into other fields with those entering psychiatry would help answer some of the questions about who is going into psychiatry and why.

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Worsening of Tourette's Disorder Due to Neuroleptic-Induced Akathisia

Peter Weiden, M.D., and Ruth Bruun, M.D.

Of 100 patients with Tourette's disorder, six demonstrated unequivocal worsening after their neuroleptic doses were increased. Akathisia was described in the records of all six patients and seemed to be the cause of the deterioration.
(Am J Psychiatry 1987; 144:504–505)

Neuroleptic-induced akathisia is a distressing side effect and has been reported to lead to suicidal behavior (1), violence (2), and worsening psychosis (3). Tourette's disorder is a nonpsychotic condition for which long-term neuroleptic treatment is indicated, and patients with this disorder are exquisitely sensitive to side effects from these agents (4). Worsening of primary symptoms due to akathisia (after an initial positive response to neuroleptics) has important management implications for Tourette's disorder and theoretical implications for the neuroleptic treatment of psychosis.

METHOD

We retrospectively examined the case records of 100 outpatients with Tourette's disorder who had been examined by one of us (R.B.). We selected the patients who exhibited either 1) an initially positive neuroleptic response that subsequently worsened at higher doses or 2) complaints of akathisia with a parallel worsening of Tourette's disorder. Six patients (6%) met the study criteria. The adults and the families of the children were contacted and interviewed.

CASE REPORTS

Case 1. Alan, an 11-year-old boy, had a 5-year history of touching, "clinging," blinking, making nasal sounds, and coughing. Tourette's disorder was diagnosed at the age of 10, and pimozide treatment (2 mg/day) was begun. Alan's initial response was moderate. A dose increase to 4 mg/day 2 months later resulted in his beginning to touch objects at dangerous heights, such as a ceiling lamp. This new Tourette's symptom was treated with an increase in pimozide dose to 6 mg/day, after which Alan would run out of his house and touch streets in front of oncoming traffic and would burn himself by touching the stove. These dramatic symptoms were accompanied by general psychomotor restlessness consistent with akathisia (no other extrapyramidal symptoms were reported). After a decrease in the pimozide dose to 3 mg/day, the dangerous touching behavior and agitation stopped, but the other Tourette's disorder symptoms (tics and chirping) worsened.

Case 2. Ms. B, a 37-year-old woman, had had classic symptoms of Tourette's disorder since the age of 6. She had developed a keen cognitive awareness of her neuroleptic side effects and was adept at changing her dose as her symptoms waxed or waned. She was most familiar with problems from akathisia. An increase in either haloperidol or pimozide dose to where akathisia developed invariably worsened her tics. At that point she immediately lowered her dose, not because of intolerable akathisia but to control her Tourette's disorder.

Case 3. Carol, a 16-year-old girl, had developed multiple tics in early childhood. At age 12 the tics increased in severity and she developed compulsive touching and demanding behavior. She was started on a regimen of haloperidol, 1 mg/day, and immediately improved. Over the next 2 years the dose was raised gradually to 6 mg/day, and Carol began to exhibit uncharacteristic restlessness and irritability. She would constantly get up and down when sitting on a chair or

Received June 23, 1986; revised Oct. 17, 1986; accepted Dec. 5, 1986. From the Tourette Clinic, Department of Psychiatry, Payne Whitney Clinic, New York Hospital-Cornell Medical Center. Address reprint requests to Dr. Weiden, Payne Whitney Clinic, New York Hospital-Cornell Medical Center, 525 East 68th St., New York, NY 10021.
Supported in part by a grant from the Stephen Levy Foundation.
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would repeatedly raise her trunk off the bed until she became exhausted and fell asleep. Her tics evolved into banging of her elbows and head to the point of injury. She rubbed her knuckles raw and pulled out her eyebrows. Her haloperidol dose was raised over the next 9 months to 30 mg/day to control these severe and escalating Tourette's symptoms. Although obviously oversedated, she screamed, tore her hair, and constantly jumped and tossed about. A reduction in haloperidol dose to 10 mg/day produced a remarkable immediate global improvement, including resolution of the compulsive touching and self-mutilation.

Case 4. Mr. D, a 19-year-old man, had had multiple tics and involuntary vocalizations since age 4. When he was 8 years old Tourette's disorder was diagnosed. He did reasonably well during his first year of treatment with haloperidol, 2.5 mg/day, but when the dose was raised to 4 mg/day he began to feel "hyper," and his tics worsened. Further dose increases, up to 6 mg/day, caused increases in tics and marked behavior problems. He could not sit still in school and had frequent temper tantrums. He felt better and his Tourette's symptoms improved when the haloperidol dose was decreased. A subsequent medication increase produced the same symptom complex. It eventually became apparent both to the doctor and to Mr. D's parents that increases of his haloperidol dose caused exacerbations of both his Tourette's disorder symptoms and behavior problems. Finally, while taking 1 mg/day of haloperidol, he was the best he had been in several years. Any further reduction in haloperidol dose brought back his initial Tourette's symptoms.

Case 5. Mr. E, a 26-year-old man, was first afflicted by symptoms of Tourette's disorder at the age of 10 and was diagnosed at 11. He did well initially while taking 3 mg/day of haloperidol. His school work improved and his symptoms were well-controlled until coprolalia appeared 6 months later, but when the haloperidol dose was increased the coprolalia became louder and more frequent. Mr. E was taken out of school, and he entered a university hospital psychiatric unit, where the haloperidol was rapidly increased to 300 mg/day. Despite (or because of) this, the coprolalia worsened. He also became very infantile, clung to his parents, and exhibited slurred speech, yet he felt constantly restless and could not sit or lie still. Over the next 6 weeks the haloperidol dose was lowered to 20 mg/day, and his restlessness and coprolalia simultaneously abated. Mr. E was able to return to a special education class in school; he did well there and excelled at sports.

Case 6. Frank, a 13-year-old boy, had had eye tics since age 4 or 5, generalized facial tics since age 7, and a wide variety of motor and vocal tics since age 10. Tourette's disorder was diagnosed and partially controlled with 0.5 mg/day of haloperidol. Shortly afterward the dose was raised to 1 mg/day. Frank's tics increased, and the dose was increased to 1.5 mg/day. The tics continued to worsen, and the haloperidol dose was raised to 3 mg/day. He then developed extreme restlessness and other side effects, including weight gain, depression, and irritability. After gradual tapering and discontinuation of haloperidol, Frank began to have fewer tics and side effects. Afterward he was treated with clonidine, which reduced his tics 60%–70%, and his symptoms never again escalated to the severity seen when he was receiving haloperidol.

DISCUSSION

The major finding of this study is that the symptoms of Tourette's disorder (including tics, coprolalia, and obsessive behavior) can worsen as the dose of neuroleptic is increased. The six patients described all had an initial positive response to neuroleptics, and as the dose was increased because of residual Tourette's disorder symptoms, they became tormented and restless. All six had akathisia, and we believe this akathisia accounted for their deterioration. The possibility of retrospective distortion of akathisia is unlikely in view of the vigor and detail with which it was reported. Although we found a 6% prevalence, a prospective study would most likely yield a higher prevalence of concurrent akathisia and deterioration.

This study demonstrates a need to diagnose and treat akathisia when Tourette's symptoms paradoxically worsen during neuroleptic treatment. It also lends indirect support to the hypothesis that unrecognized akathisia can make psychotic patients worse.

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Toxic Neuropsychiatric Effects of Digoxin at Therapeutic Serum Concentrations

Stuart J. Eisendrath, M.D., and Michael A. Sweeney, M.D.

Serum digoxin concentrations can mislead psychiatric consultants. Two patients with therapeutic digoxin concentrations were seen for neuropsychiatric disorders that cleared rapidly once digoxin was discontinued.
(Am J Psychiatry 1987; 144:506–507)

Digoxin has the potential for producing numerous neuropsychiatric side effects (1). After development of a means to measure digoxin serum levels in recent years, therapeutic ranges were established for serum digoxin concentrations, typically 0.5 to 2.0 ng/ml. These ranges were intended to maximize clinical response and minimize toxicity (2). Previous reports (3, 4) have demonstrated digoxin's potential for producing neuropsychiatric toxicity when the serum concentration is above the therapeutic range. We previously reported a case (case 1) in the cardiology literature that suggests this toxicity may also occur within the therapeutic range (5). The present report includes two cases to alert psychiatrists that a serum digoxin concentration within the therapeutic range may be associated with neuropsychiatric toxicity. Both cases featured cognitive dysfunction, depressive appearance, and emotional lability.

CASE REPORTS

Case 1. Mr. A, a 74-year-old married white man, was admitted to the urology service to have a suprapubic prostatectomy for adenocarcinoma. He was in good health before the surgery. The prostatectomy was performed without complication.

Postoperatively Mr. A developed a wound infection and was treated with tobramycin, with good results. Thirteen days after surgery he developed an episode of paroxysmal atrial tachycardia and was treated with 0.25 mg/day of digoxin. Five days after he started receiving digoxin, Mr. A was noted to have an altered mental status. He appeared confused and disoriented and was markedly anorexic. Neurologic examination revealed no focal neurologic findings. An EEG showed generalized slowing without focal abnormality. A CAT scan showed mild cortical atrophy. A neurologist felt Mr. A had possibly suffered a transient episode of hypoxia. The results of laboratory investigation were unrevealing except for a lowered serum albumin level of 3.0 g/dl, presumably related to Mr. A's poor nutritional status. His digoxin level was checked twice; both levels, 0.8 ng/ml and 0.9 ng/ml, were well within the laboratory's therapeutic range (0.5–2.0 ng/ml).

The urology staff consulted the psychiatry department because Mr. A appeared depressed, tearful, and anxious. The psychiatric consultant found that he was tearful and had marked lability of mood. He scored 14 on the Cognitive Capacity Screening Examination, on which a score of less than 20 indicates an organic mental disorder (6). He exhibited deficits in calculations, abstractions, and both immediate and remote memory. There was no evidence of hallucinations. Mr. A described his mood as "okay, but I break into tears for no reason." His wife confirmed his statement that he had had no evidence of cognitive dysfunction before entering the hospital.

Mr. A's confusion worsened, and his cognition score dropped to 10. An ECG was obtained, but it revealed no new abnormalities or sign of digoxin toxicity. The only laboratory change was an increase in his digoxin level to 1.5 ng/ml. Digoxin was discontinued to try to improve his cognition. Within 3 days he appeared more alert and stated that he had an appetite for the first time in weeks. Five days after stopping digoxin treatment, with a serum concentration less than 0.5 ng/ml, his cognition score rose to 19.

Because of his excellent progress, Mr. A was discharged to his home rather than the nursing home that had previously been arranged. Two weeks later he scored 29 on the Cognitive Capacity Screening Examination. Both he and his wife felt he had returned to his former level of mental functioning.

Case 2. Mr. B, a 71-year-old white man, had developed acute pancreatitis after a cholecystectomy. He developed a pancreatic pseudocyst that required operative drainage. During his recovery he developed an aspiration pneumonitis and congestive heart failure; the latter was treated with digoxin, 0.125 mg/day. After 1 month he was transferred to our institution. His only medications were digoxin and antacids.

The second day after Mr. B's transfer the surgical team asked for a psychiatric consultation because he appeared depressed and tearful. The consultant learned that before his recent surgery Mr. B had been in good health; he had had a left-sided stroke 11 years earlier but had completely recovered from it. He had no history of psychiatric disorder. He denied feeling depressed and said he did not know why he

Received June 23, 1986; revised Nov. 18, 1986; accepted Dec. 30, 1986. From the Psychiatric Consultation-Liaison Service, Department of Psychiatry, University of California, San Francisco. Address reprint requests to Dr. Eisendrath, Box 34-C, Langley Porter Psychiatric Institute, 401 Parnassus Ave., San Francisco, CA 94143.
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was crying so frequently. He felt optimistic about his chance for recovery. He and his wife noted that he also occasionally broke into laughter for no apparent reason.

During the psychiatric examination Mr. B did not appear depressed except when he broke into tears without any clearly identified sad thought. The labile tearfulness occurred approximately 10 times within 45 minutes. On the Cognitive Capacity Screening Examination he scored 21 out of 30. He exhibited impaired recent memory, concentration deficits, and difficulty with calculations. He and his wife confirmed that his usual mental functioning was superior before the cholecystectomy. His laboratory values were normal except for a serum albumin level of 2.3 g/dl. His digoxin level was 0.6 ng/ml.

Since Mr. B had no more evidence of congestive heart failure and the digoxin was seen as a possible contributor to his altered mental state, it was discontinued. Within 3 days his lability of affect was significantly diminished; he had one episode of tearfulness in a 45-minute session. His cognition score increased to 28. Both he and his wife felt his mental functioning had become close to his baseline. One week later, before discharge, his cognition score was 29 and he felt "back to normal."

DISCUSSION

With the advent of serum digoxin measurements, cases of neuropsychiatric toxicity appeared that involved "toxic" serum levels (2, 3). Wamboldt et al. (3) described depressive symptoms accompanying serum digoxin concentrations over 2.0 ng/ml. They suggested that the depressive picture produced by digoxin can lead an unsuspecting clinician to mistake digoxin toxicity for depression. Usually such patients' symptoms are not completely typical of true depression. Consistent with this, the tearfulness in our two patients was not accompanied by a lowered mood, pessimism, or loss of humor. Each of our patients suffered toxic symptoms at a serum digoxin concentration well below 2.0 ng/ml. Our elderly patients may have been at special risk for digitalis toxicity. Diminished renal excretion, body mass, body water, and albumin binding may produce toxicity more easily in the elderly (7).

Initial studies with serum digoxin concentrations attempted to demonstrate a correlation between serum digoxin concentration and cardiac toxicity. In one early prospective study, Beller et al. (8) found a correlation between electrocardiographic evidence of digoxin toxicity and elevated serum level. That study, however, did not show a correlation between mental status aberrations and serum levels.

Several reports have demonstrated that these ranges are of limited value in predicting cardiac manifestations of toxicity or optimal therapeutic dose. Ochs et al. (9) found that changes in serum digoxin concentration correlated poorly with most electrocardiographic variables. More important, psychiatric, gastrointestinal, and neuromuscular symptoms had little correlation with digoxin level. Von Arnim et al. (10) similarly evaluated 287 patients and found that serum digoxin level did not correlate with toxicity. These studies and our cases suggest that clinicians should not overlook digoxin as an etiology for neuropsychiatric symptoms by accepting the therapeutic range as absolute. Psychiatric consultants in particular should not dismiss digoxin as an etiology for depressive symptoms, cognitive dysfunction, or overt psychoses merely because the serum digoxin concentration is in the normal range.

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Patients With Panic Attacks and Abnormal EEG Results

Matthew J. Edlund, M.D., M.O.H., Alan C. Swann, M.D., and Jeffrey Clothier, M.D.

The authors describe a series of patients who presented with atypical panic attacks involving hostility, irritability, severe derealization, and social withdrawal. None had clear temporal lobe epilepsy but most had temporal EEG abnormalities. Although their response to treatment was unpredictable, some did well with carbamazepine or alprazolam.

(Am J Psychiatry 1987; 144:508–509)

It has long been thought that panic attacks may be caused by epileptiform or focal abnormalities of the temporal lobe (1). Recent positron emission tomography evidence points to differential blood flow of the right temporal region, as compared to the left, in subjects who panic in response to lactate infusion (2). We report here a series of cases of atypical panic attacks associated with temporal EEG abnormalities.

CASE REPORTS

Case 1. Mr. A was a 40-year-old Vietnam veteran who presented with panic attacks of 15 years' duration that were marked by severe derealization and an intense fear of death. After these attacks, he became angry, even violent, or withdrew from social contact for a period of hours to days. His panic attacks had begun on his return from the war, when he began drinking heavily, and there was a generally deteriorating social and occupational course over the next 15 years. He was hospitalized several times for alcoholic detoxification. He had a childhood history of grand mal seizures, which had been treated with phenytoin. Particularly when he was drinking and not taking anticonvulsants, he became hostile and angry and threatened to kill himself or family members. Frequent "chest tightness" and "hyperventilation" were attributed to "exercise-induced asthma."

Mr. A was hospitalized after a series of violent outbursts 2 years before consulting us. A CAT scan and an EEG showed no abnormalities, and his anticonvulsant medication was stopped. His violent outbursts then became worse, and he suffered several panic attacks per day. A repeat EEG showed brief runs of left temporal theta waves, with occasional left temporal sharp waves. A nuclear magnetic resonance procedure showed atrophic changes without focal abnormalities. Mr. A developed a rash when treated with carbamazepine. When he was given clonazepam, 10 mg/day, the panic attacks originally diminished, then recurred as before. When he did not take medication, he had one to two mild panic attacks per week.

Case 2. Mr. B, 21 years old, reported panic attacks "as long ago as I can remember." By his early teens he was experiencing circumscribed episodes of palpitations, sweating, increasing respirations, feelings of impending doom, and marked depersonalization and derealization. He found that these attacks were made worse by marijuana and improved by alcohol. After such attacks he withdrew socially. He never developed phobias, and there was no history of seizures. His parents reported that after some attacks, "he just blows up and smashes things." Hospitalized with depression during his senior year in high school, Mr. B did not respond to tricyclics but responded to phenelzine, 30–45 mg/day. Later on, his panic attacks sometimes erupted into fights with his siblings. Results of a neurological examination when he consulted us were normal; an EEG showed brief runs of left temporal sharp slowing. He initially responded to carbamazepine with few panic attacks over several weeks, but then his symptoms recurred as before.

Case 3. Mr. C, 32 years old, first had "attacks" 3 years before coming for consultation. They began with "a terrible scary feeling in my chest," followed by severe sweating, rapid breathing, and marked derealization ("I lose all track of reality—nothing seems real"). During these times, he became irritable and hostile. Mr. C had suffered a motor vehicle accident 8 years earlier, with severe head trauma. His mobility was limited by lameness following the accident, but he reported no phobias, drug or alcohol use, or history of seizures. An EEG revealed excess temporal lobe theta waves, with the right side worse than the left. Although he reported some response to lorazepam, 2 mg/day, during these "scary" periods, he found alprazolam very sedating. He responded well to carbamazepine, 400 mg/day, with a decrease in attacks from several times per week to less than once a month.

Case 4. Ms. D, a 39-year-old woman, suddenly found herself "beginning to fear people" while on a foreign trip. After returning home, she awakened in the night in acute panic, with chest tightness, warm flushes, and lightheadedness. Her worst symptoms, however, were tremor and shaking so severe that she suffered bruises, and severe derealization and paranoia. During daily attacks she became angry and irritable and occasionally had to restrain herself from attacking bystanders. After these attacks, she wanted to be "really alone—I just would not want to be around people,

Received June 10, 1986; revised Sept. 22, 1986; accepted Dec. 30, 1986. From the Department of Psychiatry, University of Texas Mental Sciences Institute, University of Texas Medical School. Address reprint requests to Dr. Edlund, U.T.M.S.I., 1300 Moorsund Ave., Houston, TX 77030.

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period." Results of a neurological examination were normal; an EEG showed rare right temporal sharp waves. She did not develop any phobias, drink heavily, or use drugs; there was no history of seizures. She was lost to follow-up before her response to medications could be assessed.

Case 5. Mr. E, a 25-year-old man, had a childhood history of jacksonian seizures that moved up from his left hand to become full grand mal seizures. Five months before seeking treatment, he began to have panic attacks with sweating, derealization ("everything appears extraordinarily vivid, much too real to be real"), and a sense of doom. During his first attack he awakened in the night shaking so violently that he first believed he was having a seizure, but he never lost consciousness. Since he first began having panic attacks he had become more irritable. When angry he sometimes noted flashing lights or a white dot in his vision, followed by the sensation of an impending panic attack, which then may or may not have progressed to a full attack. A standard EEG, as well as an EEG that was done with nasopharyngeal leads, was read as normal; he denied drug or alcohol use. His attacks responded to treatment with alprazolam, decreasing from one or two per week to none over the next 5 months.

Case 6. Mr. F, 49 years old, had undergone a leucotomy via the dorsal approach about 20 years earlier for what were later recognized as manic symptoms. His thinking was then characterized by grandiose ideas and an inability to move from one subject to another. Approximately 6 years before coming to us for treatment, he began having "the worst things I ever had": attacks of rapid heart rate, severe shaking and sweating, frightening derealization, and a feeling of rising anger. He did not act on this anger ("I'm a very peaceable fellow") but wished that there had been a punching bag about. He had no history of seizures or alcohol or drug use. An EEG revealed bilateral frontotemporal slowing. His panic attacks stopped completely during 2-month follow-up when he took carbamazepine, 1,000 mg/day.

DISCUSSION

Panic attacks are not rare. Uncomplicated panic disorder probably afflicts about 1% of the population, and agoraphobia, which is generally associated with panic attacks at some time, may afflict a further 2%–5% (3, 4). What is unusual about this group of patients with panic attacks and abnormal EEG results is the following. 1) The panic attacks were usually associated with severe derealization and sometimes with unusually severe autonomic symptoms. 2) During, or immediately before or after, the panic attacks, the patients became either highly irritable or overtly aggressive. 3) No phobias developed, but the patients often desired to be alone and withdrew socially for a period of hours to days. They did not lose consciousness. 4) The EEG abnormalities generally involved the temporal lobes, either the nondominant one or both. The EEGs of eight other patients with uncomplicated panic attacks or panic attacks with agoraphobia—but without the concurrent symptoms of irritability or severe derealization displayed by the patients described here—were normal, similar to findings in other reports (5, 6).

Regarding the genesis of these panic attacks, in some patients there was clear evidence of previous focal or generalized seizures but not partial seizures. All but one of the patients showed some response to carbamazepine or benzodiazepines such as alprazolam and clonazepam. Distinctive characteristics of the patients included a nonspecific abnormality on the EEG and atypical panic attacks, with anger, irritability, severe derealization, marked shaking or sweating, social withdrawal, and no accompanying phobias. These unusual affective and autonomic symptoms are quite different from the ictal and interictal fear often reported by patients with temporal lobe epilepsy (7). However, such symptoms in panic patients may suggest organic involvement. Particularly if there is any history of organicity, an EEG, preferably one done with nasopharyngeal leads (which is probably a more sensitive test than the standard EEGs we used), should be considered. Because tricyclics generally lower the seizure threshold, the presence of focal EEG abnormalities, especially those involving the temporal lobes, may prompt the clinician to consider first carbamazepine or alprazolam for treating such patients.

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Cognitive Style of Patients With Bulimic and Diet-Restricting Anorexia Nervosa

Brenda B. Toner, Ph.D., Paul E. Garfinkel, M.D., F.R.C.P.(C), and David M. Garner, Ph.D.

Recent studies have reported that subjects with bulimic anorexia nervosa are more behaviorally impulsive than those with diet-restricting anorexia nervosa. This study found that bulimic anorexic patients made significantly more errors on the Matching Familiar Figures Test than restricting anorexic and comparison groups. This preliminary finding leads to the speculation that bulimic patients are more cognitively impulsive than restricting anorexic patients.

(Am J Psychiatry 1987; 144:510–512)

Recent studies have demonstrated major differences between subjects with anorexia nervosa who engage in episodes of bulimia and those who consistently restrict their food intake (1). These differences include a high frequency of impulsive behavior in the bulimic anorexic patients. While investigators have commented on behavioral impulsivity, cognitive impulsivity (impulsive cognitive style) has not, to our knowledge, been studied in this group. The cognitive dimension of reflection-impulsivity has been one of the most intensively studied in developmental research; little of this research has been directed toward adult populations (2, 3). To distinguish cognitively impulsive from cognitively reflective individuals, investigators frequently use the Matching Familiar Figures Test (MFFT) (4). As operationalized by the MFFT, "fast-inaccurate" responses are associated with an impulsive cognitive style, and "slow-accurate" responses are associated with a reflective cognitive style.

Investigators have questioned the importance of response latency versus errors in defining cognitive impulsivity. Specifically, Ault (5) suggested that cognitive impulsivity in children may be more directly related to number of errors than to response speed, indicating difficulty in the problem-solving strategy used. Researchers have also questioned the adequacy of dichotomizing individuals into impulsive and reflective groups on the basis of a median split within a given sample (2).

The present communication is part of a larger study that involved the follow-up of patients with a primary diagnosis of anorexia nervosa who had been seen between 5 and 14 years earlier (6). In this report we examine cognitive impulsivity in a group of bulimic and diet-restricting anorexic patients at follow-up. We predicted that compared with the restricting anorexic group and a matched comparison group of normal-weight women, the bulimic group would make more errors on the MFFT. We further predicted that group differences would be even more pronounced in anorexic patients whose weight had been partially restored, since the potential mediating cognitive effects of starvation (7) (i.e., poor concentration, indecisiveness) would be reduced.

METHOD

Participants were divided into three groups: 1) 21 women (mean±SD age=28.6±4.0 years; mean weight, 82.8% of average) (8) previously classified as bulimic anorexic and diagnosed between 1970 and 1978 as having primary anorexia nervosa, 2) 23 women (mean±SD age=27.4±5.3 years; mean weight, 84% of average) classified as diet-restricting anorexic and also diagnosed during 1970–1978 as having primary anorexia nervosa, and 3) a comparison group of 24 female volunteers of average weight (mean, 89% of average) matched by age (mean±SD age=27.2±5.3 years), social class, and education who had no history of anorexia nervosa. The anorexic patients were classified into bulimic and restricting subtypes by their symptom picture at the initial consultation between 1970 and 1978. Bulimia was defined as an abnormal increase in one's desire to eat, with episodes of excessive ingestion of large quantities of food, which the person viewed as ego-alien and beyond her control (9). Anorexia nervosa was defined according to modified criteria of Feighner et al., as described previously (9).

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Supported by a research fellowship from the Ontario Mental Health Foundation to Dr. Toner and by Ontario Mental Health Foundation grant 866-83/85.

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TABLE 1. Mean Number of Errors and Average Response Latency on the Matching Familiar Figures Test of Bulimic Anorexic, Diet-Restricting Anorexic, and Comparison Subjects

Group	Number of Errors		Response Latency (seconds)	
	Mean	SD	Mean	SD
Bulimic anorexic patients (N=21)	10.3	6.7	51.6	20.5
Diet-restricting anorexic patients (N=23)	6.2	4.3	53.5	26.1
Comparison subjects (N=24)	5.4	5.4	53.1	21.9
Bulimic anorexic patients with partial weight restoration (N=12)	12.4	6.2	44.9	15.9
Diet-restricting anorexic patients with partial weight restoration (N=17)	5.7	4.0	54.1	27.1

The MFFT was administered individually to all participants by one of the investigators (B.B.T.) according to standardized instructions (4). This investigator was blind to the patients' anorexic subgroup. The test involves simultaneous presentation of a figure (e.g., a boat) with eight different facsimiles. On each of the test's 12 items, the participant is asked to select the one that exactly matches the standard. Dependent measures included the total number of errors and the average time to the first response.

RESULTS

A one-way analysis of variance (ANOVA) indicated overall group differences among bulimic, restricting, and comparison groups for number of errors ($F=6.4$, $df=2, 65$, $p<.01$). Comparison of group means (table 1) indicated that the bulimic group made significantly more errors than the restricting anorexic group ($t=2.8$, $df=42$, $p<.01$) and the comparison group ($t=3.4$, $df=43$, $p<.001$). A one-way ANOVA did not indicate group differences for average response latency ($F<1$).

A similar pattern of results emerged when we performed a separate one-way ANOVA on the results of anorexic subjects whose weight had been partially restored (operationally defined as maintaining 80% of the Canadian average weight for their sex, age, and height) (8). The anorexic groups with partial weight restoration included 12 bulimic and 17 diet-restricting patients. Again, ANOVA indicated overall group differences for numbers of errors ($F=12.0$, $df=2, 50$, $p<.0001$). Comparison of group means indicated that the bulimic anorexic group made significantly more errors than the restricting ($t=4.2$, $df=27$, $p<.001$) and the comparison ($t=4.6$, $df=34$, $p<.001$) groups.

DISCUSSION

The present research found that the bulimic anorexic group made significantly more errors on the MFFT than the restricting anorexic and comparison groups. This finding suggests the possibility that the bulimic anorexic group was more cognitively impulsive than the restricting anorexic and comparison groups. However, this interpretation remains speculative, since cognitive impulsivity was measured only one time (i.e., 5–14 years after the original subgroup classification). To make a stronger argument for cognitive impulsivity, future studies will need to measure the consistency of cognitive impulsivity over time in a repeated measures design. Since alternative forms of the MFFT have not been developed, testing periods should be sufficiently temporally separated to ensure independence. Moreover, while studies with children have documented that cognitive ability (i.e., IQ score) accounts for no more than 10% of the variance in MFFT performance (2), future MFFT studies with adults would be improved by the addition of a measure of cognitive ability to rule out this potential confound. In addition, future researchers would be well advised to consider the effect on cognitive impulsivity of other variables that have been associated with these eating disorders, such as episodes of binge eating, vomiting, laxative and diuretic abuse, behavioral impulsivity, depression, anxiety, and obsessive-compulsive behavior.

As this study represents the first attempt that we know about to investigate cognitive impulsivity in bulimic anorexic subjects, future research is needed to replicate our findings. Despite the limitations we have mentioned, the finding that the bulimic anorexic group made twice as many errors on the MFFT as the restricting anorexic and comparison groups is of interest from a theoretical and therapeutic perspective. Ault (5) suggested that a large number of errors reflects the difficulty impulsive children have in using effective problem-solving strategies. Developmental literature (10) suggests that training techniques which emphasize scanning strategies have been more successful in reducing error rates than techniques which inhibit rapid responding. It would be interesting to investigate whether bulimic anorexic subjects use problem-solving strategies similar to those of impulsive children and whether training in scanning strategies could reduce errors. The present finding that the bulimic anorexic group may be more cognitively impulsive than the restricting anorexic group adds further support for the distinction between bulimic and restricting subtypes of anorexia nervosa reported in the literature (1).

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Lateral Ventricular Size and Social Network Differentiation in Young, Nonchronic Schizophrenic Patients

Larry J. Seidman, Ph.D., Robert L. Sokolove, Ph.D., Christine McElroy, Ph.D., Peter H. Knapp, M.D., and Thomas Sabin, M.D.

The authors correlated lateral cerebral ventricular size with social network differentiation and social outcome in 15 young, nonchronic patients with schizophrenia and schizophreniform disorder. Patients with fewer social contexts, fewer types of relationships, and less independent residence had larger ventricles.

(Am J Psychiatry 1987; 144:512–514)

Brain impairment in schizophrenia has been demonstrated by multiple techniques (1). Enlargement of the lateral cerebral ventricles determined by computer tomography is one of the most consistent abnormalities (2). Lateral ventricular enlargement correlates positively with neuropsychological impairment, "soft" neurologic signs, poor premorbid social and school adjustment, and poorer responses to antipsychotic medications (1, 2).

Attempts to codify social factors associated with schizophrenia have focused on the number and types of social relationships and interactions in the community (3). Hammer (3) suggested that the structure of social networks may be the most fruitful variable to analyze in the social environment of the schizophrenic patient.

In this pilot exploration, we studied the relationship between structural brain abnormality and social functioning in patients with schizophrenia and schizophreniform disorder. We hypothesized that those patients with ventricular enlargement would have less differentiated (less complex and elaborate) social networks and less independent social functioning.

METHOD

Subjects

Fifteen patients (mean age, 23.5 years) participating in the Interhospital Study of Psychotherapy of Schizophrenia (4) were subjects. They gave informed consent to have CAT scans and social network interviews. They were selected because they were young and had midrange prognoses, so the impact of institutionalization and chronicity on the network measures could be minimized.

The participants spoke English fluently and were free of gross brain damage, alcohol or drug abuse, and

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Supported in part by NIMH Small Grant Award MH-37156 to Dr. Seidman and NIMH grant MH-26183 to Dr. Knapp.

The authors thank Ms. Deborah Rothstein for making *DSM-III* diagnoses and ventricular measurements, Drs. Gordon Sherman and Albert Galaburda for help in using their planimetry equipment, Dr. John Gunderson for referral of some patients, and Dr. Steven Faraone for help in statistical analyses.

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handicapping physical illness. None had received ECT, was pregnant, or had a postpartum psychosis or brief schizophrenic-like psychosis.

Eight men and seven women participated (five black, 10 white). All had completed the ninth grade (mean educational level, 12.1 grades). Twelve were right-handed, one was left-handed, and two had mixed handedness. The evaluation took place approximately 2 years after the first psychiatric hospitalization (range, 11–60 months). They had a mean of 2.1 hospitalizations (range, 1–5). The average lifetime sum of all hospitalizations was 6 months (range, 1–11 months). The longest continuous hospitalization was 7 months. Thus, the subjects were young, relatively well-educated, and not chronically ill.

Procedure

The interhospital study (4) diagnoses of schizophrenia had been based on *DSM-II* criteria, since the patients had been admitted into that study between 1975 and 1982. We blindly rediagnosed all 15 subjects by using *DSM-III* criteria in a post hoc chart review. Eleven of the patients were rediagnosed as schizophrenic, and four had schizophreniform disorder.

The patients received noncontrast CAT scans, and the measure of lateral ventricular size, the ventricle-brain ratio (VBR), was computed by means of the method described by Weinberger et al. (2). The body of the lateral ventricles and the inner table of the skull were measured three times with a Zeiss MOP-3 planimeter. Excellent interrater reliability was established ($r=.98$, $p<.00001$), and blind measures were used.

Social network information was blindly collected during a tape-recorded semistructured interview using a modification of the Network Analysis Profile (5). The study used a subjective personal network strategy (6), which involves choosing a starting unit (the subject) and obtaining a list of all others whom the subject knew by name and had directly contacted during the 3 months before the interview.

"Network differentiation" (complexity and elaboration) was measured by 1) *types of contexts*—the number of social contexts, such as home and church, in the network—and 2) *types of relationships*—the number of relationship types, such as family and friend, in the network. A third variable, *network size*—the total number of people encountered by the subject—was not considered a measure of differentiation.

We studied additional variables that might clarify our primary hypothesis. These included two objectively determined outcome variables: 1) degree of independent living and 2) total number of inpatient and partial hospitalization days. We also examined neuropsychological performance on the Wechsler Adult Intelligence Scale, Visual-Verbal Test, Wisconsin Card Sorting Test, Porteus Mazes Test, Continuous Performance Test, and Trail Making Test (7). Finally, we blindly rated the patient's motivation during neuropsychological testing.

TABLE 1. Ventricle-Brain Ratio (VBR), Social Network Data, and Neuropsychological Performance of 15 Young, Nonchronic Schizophrenic Patients

Variable	Range	Mean	SD
Age (years)	19–41	23.5	5.4
VBR	1.2–18.3	7.9	4.5
Social network variables			
Number of people in network	9–97	44.9	24.5
Number of relational types	2–14	9.7	3.2
Number of types of contexts	2–17	10.7	3.5
Neuropsychological variables			
Wechsler full-scale IQ	77–130	104.8	14.3
Wisconsin Card Sorting Test categories	2–6	4.5	1.5
Visual-Verbal Test total errors	3–31	16.7	8.7
Porteus Mazes Test quotient	42–132	99.4	30.5
Continuous Performance Test omissions (%)	0–7.7	1.93	2.21
Trail Making Test B time (seconds)	52–210	87.9	39.7

The data were analyzed with the Pearson product-moment and Spearman correlations (motivation data).

RESULTS

Table 1 shows the patients' mean age, VBR, social network data, and neuropsychological performance. Patients with larger ventricles had a smaller number of social contexts ($r=-.49$, $p=.03$) and fewer types of relationships ($r=-.48$, $p=.04$). Patients with larger ventricles were also more likely to be living in mental health residences than independently ($r=-.58$, $p=.01$), and a trend ($r=.39$, $p=.09$) indicated that patients with larger VBRs had more inpatient and partial hospitalization days.

Ventricular size was unrelated to network size ($r=.12$), age ($r=-.04$), sex ($r=-.06$), or race ($r=.06$). Social network variables were unrelated to age, chronicity, frequency of hospitalization, or length of hospitalization ($r<.20$ in all cases). There was no relationship between VBR or social network measures and 12 neuropsychological variables. Only two of 48 correlations in this matrix were significant. There was no relationship between VBR and motivation ($r_s=-.23$) or between motivation and either number of social contexts ($r_s=.14$) or number of relationship types ($r_s=.14$).

DISCUSSION

Our basic hypothesis was confirmed: ventricular enlargement was associated with limited social network differentiation. This subjectively determined characteristic was buttressed by the objective findings of greater use of sponsored housing and longer hospital stays. The findings could not be explained by demographic factors, chronicity, neuropsychological impairment, or low motivation.

Although network dedifferentiation may be the consequence of "negative" symptoms, it also could result

from the isolating paranoia of "positive"-symptom schizophrenia. Since support for the hypothesized relationship between negative symptoms and high VBR is surprisingly sparse (8), it is premature to conclude that social network dedifferentiation simply reflects negative symptoms.

A critical problem posed by our method is the reliance on a self-report interview of psychiatric patients to define social network structure. The degree to which subjectively perceived network characteristics measure actual social reality is unknown (3); however, the fact that larger VBRs correlated with objectively determined social outcome measures and with differentiation characteristics of social networks (not with total size) provides preliminary confirmation that we accurately measured identifiable features of social networks. This method allows us to go beyond simply saying that patients with ventricular enlargement are "sicker" or "more socially impaired"; it starts to specify the kind of social impairment.

Our sample included schizophrenic patients and patients with schizophreniform disorder. There is evidence that these patient groups have similar CAT scans (2) and clinical outcomes (9). Moreover, the relationship between ventricular enlargement and social functioning is not necessarily specific to schizophrenia. Ventricular enlargement determined with pneumoencephalography has been shown to correlate with degree of overall adaptive impairment at work and in social life for patients with other illnesses (10). Future studies should cross-validate these findings with larger samples of normal and psychiatric comparison groups and should use data from multiple network perspectives. Bringing together precise measures of brain function and social function has considerable promise in the study of schizophrenia.

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On-Site Job Bank at the 1987 Annual Meeting

The American Psychiatric Association will sponsor an on-site job bank at the annual meeting in Chicago, May 9–15, 1987, where employers and applicants may register their listings. The fee is $30 for an employer listing and $10 for an applicant listing. Forms may be obtained by writing to Susan Lash, Program Assistant, APA, 1400 K Street, N.W., Washington, D.C. 20005, or by calling (202) 682–6173.

Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

PSYCHIATRY UPDATE

Psychiatry Update: American Psychiatric Association Annual Review, vol. 5, *edited by Allen J. Frances, M.D., and Robert E. Hales, M.D. Washington, D.C., American Psychiatric Press, 1986, 765 pp., $49.95; $36.95 (paper).*

By the time you read this, 1986 will be last year, and the American Psychiatric Press will be advertising the 1987 *Annual Review*. The topics for 1988 have already been selected. Lest the 1986 *Annual Review* slip too quickly into obscurity, I hope this review will guide the reader to a fresh yet scholarly volume that reviews six topics of relevance to most psychiatrists: schizophrenia, drug abuse and drug dependence, personality disorders, adolescent psychiatry, psychiatric contributions to medical care, and group psychotherapy. For those readers who are not familiar with the *Annual Reviews*, some orientation may be helpful. The volumes have appeared annually for the past 5 years, the last two under the editorial leadership of Allen J. Frances and Robert E. Hales. There is no attempt to make this a yearbook updating progress in the field over the past year. Rather, these reviews examine the present state of the field, with consideration of both recent and past accomplishments. Although the volume itself is a hefty 765 pages plus a 23-page index, the six sections each comprise about 130 pages divided into five or six chapters with an introduction and an afterword by the section editor. If the reader approaches the *Annual Review* as six short books, then the length may seem quite comfortable. The treatment of each topic is more comprehensive than it would be in a journal review article and yet not overly expansive, as it would inevitably be in a single volume. The use of five or six authors allows for different aspects of each field to be illuminated, much as in a symposium of the annual meeting. I found that the sections farthest from my usual interests were the most stimulating. The length of each chapter is too short to add much to the knowledge of someone who carefully follows the literature in his or her own field but ideal for combating the subspecialization that inevitably narrows us all.

All the reviews seem thorough and scholarly, but it is the sense of advocacy in some sections that makes them most appealing, especially to the nonexpert. The demand of the adolescent psychiatrists for more attention to accurate diagnosis of affective disorder and the insistence by the group therapists on more integration of their discipline with psychiatry give the reader a point of view to ponder while reading each chapter. Although forceful statements of position by the section editors might detract a bit from scholarly caution, they make the reading much more directed and purposeful. Both the introductions and the afterwords for each section should be used to raise controversies that readers can try to resolve for themselves as they read each chapter.

The American Psychiatric Association has fussed with the title for these volumes, switching from *Psychiatry 1982* to *Psychiatry Update*. I sympathize with the attempt to convey timeliness without connoting ephemeralness. Topics are not generally repeated from year to year, so that one could just as profitably read any of the other years' volumes in 1987. Psychiatrists have long been interested in the intersection between timeliness and timelessness, so perhaps the title will not mislead them about the value of this volume.

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PSYCHOTHERAPY

Theaters of the Mind: Illusion and Truth on the Psychoanalytic Stage, *by Joyce McDougall. New York, Basic Books, 1985, 320 pp., $22.95.*

This book, which boasts a highly laudatory foreword by the eminent Dr. Otto Kernberg, will be rejected by a substantial number of practicing American psychiatrists. That does not mean it is a bad book, only that a certain mental set is necessary to read it. I will first discuss the reasons why many will reject it and then point out its contribution. Due to shortage of space I can offer very little direct quotation, and I will indicate other documentation only by page number.

First, biologically oriented psychiatrists will reject the book on the grounds that agoraphobia and panic disorders are discussed strictly as if they respond to psychoanalysis, whereas the average practitioner these days would be inclined to reach for imipramine or propranolol for the typical patients described on pages 28 and 41. Some extraordinary claims are made to explain many psychosomatic disorders—for example, "Her skin allergies were doubtless a primitive, preverbal kind of protection against the loss of her body limits, as well as a response to her intense desire for fusion with the archaic mother-image of the past" (p. 35). At one point (p. 53) we are advised "perhaps" to "listen to the rhinencephalon." On page 113 a deliberate aggregation is made between the usual psychosomatic maladies and anxiety and depressive states without reference to the vast research literature distinguishing these states biologically and in their response to various pharmacologic agents. There is an interesting section on alexithymia.

Second, psychiatrists and psychoanalysts who like metapsychological precision will be unhappy with the confusion of concepts that abound in the book (as well as the author's blurring of the *DSM-III* categories). For example, self-representation, self, ego, "I," "the many Is contained within each patient's official I" (p. 15), "ego identity" (p. 43), "basic identity" (p. 126), and "the agency called the ego" (p. 286), as well as various forms of "self" and "I," are scattered all over the book with little careful metapsychological discussion or delineation. This may involve a translation problem, for which the publishers are at least partly to blame—we are not told who translated this book from the original French 1982 volume entitled *Théâtres du Je*. I do not think the English translation of the title and subtitle gives any

notion of what the book is about. Borrowing from the French psychoanalytic tradition, I think that *Theaters of the "I"* would more accurately portray the focus of the book. It is not clear where the subtitle came from.

I will try to show below that McDougall's main contribution has to do with the study of "I" as a concept loosely and metaphorically applied. She studies the various representations of "I" formed developmentally and in the interaction with significant others as they present themselves in the psychoanalytic situation.

Although the book is Freudian in its essence, stressing liberation by knowing the truth as the crucial element in psychoanalytic cure, it will not be acceptable to most American Freudian or neo-Freudian psychoanalysts because it leans most heavily on Kleinian theory and interpretations, and I mean Klein's original formulations, not those of Kernberg. As McDougall describes it (p. 19), her "horizon" opened for her on reading Klein's *The Psycho-Analysis of Children* (1). (This seems to have happened for a number of European psychoanalysts [2].) The Kleinian orientation is stressed repeatedly (pp. 78, 173, 204) in no uncertain terms. Quoted interpretations by the author that are strictly in Kleinian terminology abound (for example, on pp. 35, 45, 67, and 133), and a quasi-Kleinian notion of the death instinct is advocated (p. 126). However, the book is a theoretical hodgepodge, containing echoes, sometimes with and sometimes without attribution, of authors such as Groddek (pp. 12, 53), Lacan (pp. 89, 111), Bion (pp. 134, 204, 222, with attribution), and even Heidegger (in her use of the term "ec-static states"). The one cryptic reference to Sartre (p. 16), who had much to say on McDougall's subject, is to a bibliographic reference listed out of place alphabetically (p. 292).

The author refers to Freud's structural theory as his "personal poetry" (p. 219) and, as might be expected, definitively prefers Kernberg's views on narcissism to those of Kohut, although her criticisms of Kohut are primarily of his early views (3). There is a disconcertingly optimistic tone to the author's extremely hopeful expectations for her version of psychoanalysis, even for the most serious psychotic and psychosomatic disorders, a set of expectations that tends to be found more in the early psychoanalytic writers and led to unnecessary and unfortunate disillusionment.

In spite of all this I found the book creative and interesting. The epilogue, which the publishers should have placed at the beginning of the book, even before the foreword, serves as an excellent orientation to McDougall's contribution. It begins by defining psychoanalysis as "a theater on whose stage all our psychic repertory may be played. In these scenarios the features of the internal characters undergo many changes, the dialogues are rewritten and the roles recast" with the purpose of leading analysands to the discovery of their internal reality and their inner truth, "once all the different parts of themselves and all the people who have played important roles in their lives have had a chance to speak their lines" (p. 284). The author ignores the exciting epistemological issues here. For example, Lacan might argue that there is no inner truth and Derrida might add that there is no inner reality either—there is only the play or scenarios or dialogues. Although the author, a supervising and training analyst at the Paris Psychoanalytic Society writing in the French tradition, is surely familiar with all this, she maintains her definition consistently throughout, without noting that it, along with her entire theatrical metaphor of truth and illusion and the various selves or "I"s of the subject, easily could have been written by Nietzsche (4).

McDougall's central contribution, then, revolves around her metaphor of the theater and the question of what is illusion and what is truth. She does give attribution to Pirandello, who was one of the first modern playwrights to stress this problem (although it is found from time to time throughout the history of drama—in Sheridan's *The Critic* [1779], for example). What McDougall does is rewrite the description of the psychoanalytic process using this metaphor consistently throughout, and of course this lends itself best to theories stressing the projection of split-off self and object representations. However, it also stimulates thinking about the dialectical process involved in the search for "truth" and contributes a metaphor that nicely ties together the communicative aspects of psychological productions—whether creative, average, or pathological—and psychosomatic phenomena of all sorts as they appear in the consulting room. All of this has a Lacanian echo, but if one is willing to join in the play, as McDougall urges, one cannot help but be instructed and edified by her drama and emerge improved in psychoanalytic listening.

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The Psychodynamics of Medical Practice: Unconscious Factors in Patient Care, *by Howard F. Stein. Berkeley, University of California Press, 1985, 185 pp., $16.95.*

If it is the reviewer's usual task to advise his or her audience on whether to read the book being considered, this volume invites a different question—whether the interested reader should take up this book or, rather, read (or reread) its predecessor, Michael Balint's *The Doctor, His Patient and the Illness* (1). Stein correctly places his book in the tradition inaugurated by Balint with the publication of his seminal work in 1957. A comparison of the two is thus inevitable, and I am led to question what territory Stein is opening up that Balint has not already explored and staked out.

The subject matter is broadly the evaluation and treatment of emotional factors in general medicine. It is commonplace that medical conditions are often highly influenced by (usually unconscious) emotional factors, that patients often bring emotional conflicts to their physicians in the guise of medical complaints, and, finally, that the outcome of the patient-doctor contact is affected both by the expectations—often unconscious and transferential—that the patient has of the doctor as well as by the attitude—often unconscious and countertransferential—that the doctor has toward the patient. Can one train the medical doctor to recognize and deal appropriately with these issues? Can one train him or her to incorporate basic psychotherapeutic principles into practice? These are the questions which both Balint and Stein confront.

It must be said that in this area Balint's classic is a tough act to follow. Even after 30 years, and with the necessary translations one must make from the categories and terminology of the British National Health Service, his book remains fresh and illuminating. His method was to meet on a weekly basis with a group of general practitioners in a setting of open-ended group supervision. Out of these meetings evolved a volume that is clear, organized, and free of unnecessary psychoanalytic jargon and that presents systematically a description of how the patient "organizes" an illness to "present" to the doctor, an analysis of the institutional resistances to recognition of the patient's covert problem, guidelines for engaging in psychotherapy in the context of medical practice, and, finally, general chapters on the major issues of physician psychotherapy.

While Balint's orientation was that of a psychoanalyst with an interest in general medical practice, Stein's is that of a medical anthropologist who has worked in training programs for family practice physicians and who approaches his work as an ethnographer immersing himself in the daily routines of an alien tribe. His contacts with his subjects are through a variety of case conferences and informal, personal conversations. Unlike Balint, he focuses on a specific aspect of the psychodynamics of medical practice, that of physician countertransference. Through his conversations with the practitioners he is able to elicit a range of personal countertransference reactions to patients and their illnesses that is missing in Balint's book. His training in medical anthropology also alerts him to institutional countertransferential attitudes that dovetail into the physicians' personal responses. While Balint was primarily interested in the teaching of office psychotherapy, Stein, in his book, focuses more attention on sensitizing the physician to how personal countertransference interferes with treatment of medical illness.

There are several problems with Stein's book. Heading the list is his abandonment of simple language for the intricate distinctions between externalization, projection, and projective identification. The psychiatrist will find this discussion oversimplified, and the general physician will find it quite baffling. Who indeed is the putative reader of this book? A second problem is that of examples which are not always convincing. A whole chapter is devoted to a young adult with diabetes who seemed to suffer from rather massive personal psychopathology. This patient appeared to do quite well on his own in promoting his illness, and Stein's argument for a significant contribution through physician countertransference seems gratuitous. Finally, the narrow concentration on physician countertransference and the rather haphazard assembling of the various countertransference reactions make for a somewhat unbalanced view of the psychodynamics of medical practice. I would plead for more organization and more balance.

Admittedly it is a dirty trick on an author to build a review of his book around a comparison with a known classic. In this case Balint's work will remain the classic. Stein's book may be read for its emphasis on one aspect of Balint's general theme.

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The Quiet Profession: Supervisors of Psychotherapy, *by Anne Alonso. New York, Macmillan, 1985, 168 pp., $22.50.*

In this concise and lucid volume, Dr. Alonso has encompassed and synthesized a rich experience and has reviewed the process, problems, and pleasures of clinical psychotherapy supervision. She begins by defining the nature of supervision and those who work at it—who they are, what they do, and their relationships with those they teach.

In her delineation of the theoretical and operational paradigms used by supervisors, she separates cognitive from emotional concepts and then provides an integration of these perspectives, clarifying the role of the supervisor but leaving enough ambiguity to permit the emergence of the individual creativity inherent in the process. Her clinical examples are clear and well constructed. They enable both supervisor and supervisee to look at their relationship as well as at their work and understand the journey they must take together.

Dr. Alonso also considers other roles of the supervisor. She indicates that the supervisor must be a "teacher, a mentor, an administrator, a role model, a disciplinarian, and parental-like in his/her regard for the supervisee." In exploring these multiple roles, she looks at the conflicting needs of both supervisor and supervisee and how the gap between the two is bridged. She describes sources of difficulty that may impair the effectiveness of a supervisor: 1) the need to be admired, 2) the need to rescue, 3) the need to be in control, 4) the need to compete, 5) the need to be loved, 6) the need to work through unresolved previous conflicts in the supervisor's own training experience, and 7) spillover from stress in personal or professional life. After providing excellent clinical examples, Dr. Alonso proceeds to consider special circumstances in supervision, including the supervision of modalities other than individual therapy, supervision across professional disciplines, and supervision across age and gender barriers.

In detailing the supervisory encounter, Dr. Alonso carefully delineates the phases. She also provides an excellent supervisory evaluation form, which probes deeply into the supervisory interaction and asks for an evaluation of the trainee's capacity to form an alliance, his or her level of sophistication and "psychological mindedness," his or her ethics, and administrative issues like punctuality and record keeping. Dr. Alonso asks the supervisors to focus on performance, relationships, and ability to work within the constraints of a system. She also suggests that recommendations for future supervision and programmatic planning are helpful.

Dr. Alonso also describes a model program for psychotherapy supervisors. This program acknowledges current limits and pressures and focuses on the appropriate use of supervisors, as well as their care and feeding. Finally, an excellent bibliography is provided.

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BEHAVIOR AND GROUP THERAPY

The Theory and Practice of Group Psychotherapy, 3rd ed., *by Irvin D. Yalom. New York, Basic Books, 1985, 575 pp., $22.95.*

It hardly seems like 17 years since the first edition of Yalom's excellently written and highly acclaimed text on

group psychotherapy appeared in 1970. The second edition appeared in 1975, and now it has been reissued and updated in a third edition. I can well appreciate Yalom's statement in the preface: "It was with some reluctance that I undertook the considerable task of revising this text." The meaning I decipher from this statement is that it is indeed difficult to improve on an already outstanding piece of work. Furthermore, for a writer, it is easier to produce an original work than to modify and revise material that has already been written. The intent of the third edition is to update coverage of the field, to include new research evidence, to remove what has become outmoded and outdated, to add new clinical material from Yalom's own work, and to assure that this impressive text truly reflects the current state of the art of group psychotherapy.

I read this book from the perspective of an experienced group psychotherapy practitioner. Having not read the Yalom book for years, though recommending it highly to all of my students, it was a great refresher experience for me to take the time to reread the text in its entirety and to encounter so much familiar material. Much of this material has become the basis for my courses in group psychotherapy and supervision of students, not to mention its being the bedrock for my own clinical practice and ideas about the conduct of group psychotherapy. It is clear that I am in Yalom's debt for much of the way I think and how I conduct group psychotherapy.

I find myself pondering the question of what it is about this text that makes it so influential in shaping the practitioner. Several thoughts come to mind. A constant theme running throughout the text is the relationship between research findings and clinical practice. Suggestions to the practitioner regarding how to practice the art of psychotherapy are consistently derived from implications of research studies. One of the new areas that receives considerable emphasis in this revised edition is the demonstrated clinical usefulness of pretherapy training of group psychotherapy applicants. Another consistent theme of the book is to be practical and pragmatic. So many psychotherapy texts present a theoretical model and perhaps deal briefly with the issue of selection of clients and termination of therapy, but the really important work, the process and conduct of psychotherapy, is glossed over. This does not occur with Yalom. Group psychotherapy innovations for the practitioner described in this text are the regular use of the written summary and the value and pitfalls associated with therapist transparency and therapist self-disclosure.

Another strength of the book that I found enjoyable was the manner in which Yalom incorporates material from his other books. In the chapter on therapeutic factors there is some material from *Existential Psychotherapy* (1). In the discussion of psychotherapy outcome and differing therapists and patient perspectives, Yalom includes material from *Every Day Gets a Little Closer* (2). Ample material is included from *Encounter Groups: First Facts* (3) as process research applications for leader behavior in group psychotherapy. In the all-new chapter 15, entitled "The Specialized Therapy Group," Yalom differentiates the unique characteristics of inpatient group psychotherapy from outpatient group psychotherapy by including considerable material from *Inpatient Group Psychotherapy* (4).

Not much more needs to be said. The definitive text on the conduct of group psychotherapy has only gotten better for its updating and refurbishing. The end result is a delightful meld of new thoughts and new ideas with already existing suggestions and ideas from the previous editions. Readers with any interest at all in the field of group psychotherapy should take the time to read this newest edition. They will definitely find it worthwhile.

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Handbook of Clinical Behavior Therapy With Adults, *edited by Michel Hersen and Alan S. Bellack. New York, Plenum, 1985, 732 pp., $75.00.*

We now have a new handbook by Hersen and Bellack. Ordinarily, referring to this work as the "Hersen and Bellack handbook" might be sufficient identification. This is not the case, however, with Hersen and Bellack (or, conversely, Bellack and Hersen). Between them, these two prolific authors and editors have produced numerous edited books, many of them called "handbooks." For Hersen alone, the last count of books known to me was 35, but that was several months ago and undoubtedly is out of date. Since these editors par excellence long ago ran out of hands with which to display their handbooks, many of them on behavior therapy, the most natural question crossing any reviewer's mind is the novelty or originality of this most recent handbook. Can there really be any useful or original theme around with which to organize yet another collection of chapters? Fortunately for psychotherapists everywhere the answer is yes, since this book illustrates the application of a mature behavior therapy that has evolved into a clinical approach suitable for handling the type of difficult and complex case that might have overwhelmed behavior therapy in its adolescence. Rather than focusing on superficial, narrowly defined problem behaviors or dry descriptions of techniques, as has been the case with so many books on behavior therapy, this book delves into the nuts and bolts of clinical practice. The theme of this book is the practice of behavior therapy with adults presenting with various problems, and therefore the chapters are organized around disorders rather than techniques. Of necessity, a given disorder might require a creative combination of behavioral techniques.

The chapters in this handbook follow a specific outline, consisting of 1) introduction and description, 2) assessment, 3) range of treatment techniques available, 4) limitations and problems with the techniques, 5) illustrative case studies with actual therapist-patient dialogue when available, and 6) problems encountered during the course of treatment. The book is divided into five general areas: Anxiety Disorders, Depression, Behavioral Medicine, Schizophrenia, and a fifth, "catchall" category entitled Special Problems. Chapters are somewhat unevenly distributed across these areas.

Anxiety Disorders consists of five chapters roughly corresponding to *DSM-III* categories. All of the contributors are

well-known clinicians and investigators, and some of the chapters are by leading clinical researchers, such as Dianne Chambless on agoraphobia and Jonathan Grayson, Edna Foa, and Gail Steketee on obsessive-compulsive disorder. While some chapters stick to *DSM-III*-defined disorders, others go beyond their *DSM-III* counterparts, sometimes in a creative way. For example, Walen's chapter on social anxiety encompasses not only social phobia but also behaviors and emotions that might be classified under avoidant personality disorder. This section contains additional chapters on stress and generalized anxiety disorder and simple phobia.

The section on Depression, on the other hand, consists of only two chapters, with no further breakdown into different subcategories. Hollon and Jacobson describe the well-known cognitive-behavioral therapy often used with major depressive episodes, while Becker and Heimberg discuss social skills training in the context of their own research on dysthymia.

The section on Behavioral Medicine contains a mélange of seven chapters with topics ranging from eating disorders such as obesity and anorexia nervosa to headache and pain. Chapters on substance abuse as well as insomnia are included in this section, along with a chapter on behavioral approaches to cardiovascular disorders.

The section on Schizophrenia is divided into two chapters, one on inpatient and one on outpatient approaches. The inpatient approaches include the well-known and successful behavioral program devised for patients with chronic schizophrenia. The particular version described is a program that was developed by James Curran and his colleagues at Brown University. Similarly, successful problem solving and social skills training approaches for outpatients with schizophrenia are described in a chapter by Kelly and Lamparski.

As might be expected, the section on Special Problems contains a variety of chapters that do not fit in other sections or, for that matter, with each other. Along with chapters on marital and sexual dysfunction are found chapters on work and study problems, sex role considerations for behavior therapists, and unassertiveness. Readers might be particularly interested in the chapter on aging, a topic seldom seen in books such as this, as well as a chapter on anger and violent behavior that would have special application for those clinicians working with patients with borderline disorder.

Naturally, only a sampling of the disorders confronted by the clinician are to be found in this book. Furthermore, it is not clear why some topics are chosen and others not. For example, chapters on work and study problems and sex role considerations in therapy, although well done, seem a bit out of place, particularly when so many other clinical disorders that could have been the basis for additional chapters are not included. Finally, the organization of these chapters will provide the practicing clinician with a taste rather than a feel for clinical behavior therapy. Clearly, the editors opted to cover a greater number of problems at the expense of extensive coverage of fewer problems. This becomes most evident in the case illustrations in each chapter, many of which are limited to two or three pages in length. Nevertheless, this book will prove extremely valuable for practicing clinicians looking for new ideas and new approaches to integrate into their treatment programs.

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PHARMACOLOGY

A Primer of Drug Action, 4th ed., *by Robert M. Julien. New York, W.H. Freeman and Co., 1985, 296 pp., $22.95; $14.95 (paper).*

This is the fourth edition of a popular book on psychoactive drugs that has been written for an audience of medically and scientifically trained professionals and those without a formal scientific background. The initial chapter and the appendixes that discuss the pharmacology and neurobiological activity of psychoactive drugs in nontechnical terms are superb. Indeed, these provide an excellent review for psychiatrists who have been intimidated by the recent explosion of neuropharmacology publications.

The remaining chapters discuss psychoactive drugs that are subject to recreational use and abuse: sedative-hypnotics, alcohol, stimulants, opiates, psychedelic drugs, and marijuana. The author, a pharmacologist and anesthesiologist, attempts rationally to discuss the effects of these drugs on somatic and CNS functioning without making moral judgments or preaching. The chapters are lucid, informative, and, unfortunately, somewhat dry. There is considerable scientific information in them, including structural formulas, which may be too technical for the untrained reader despite the author's stated intentions. Like the introductory chapter and the appendixes, however, these chapters are wonderful reviews for the practicing psychiatrist who is not up-to-date on drugs of abuse. A chapter on drugs, fertility, and birth control, although seemingly out of place in this book, is also a worthwhile review of the effect of psychoactive drugs on the menstrual cycle and on male sexual behavior.

Chapters on lithium and antidepressants are included as well as a chapter on antipsychotic medication. These are less successful and contain errors that reveal the nonpsychiatric training of the author. For example, cyclic antidepressants are included as central stimulants, and amoxapine is listed as having antipsychotic effects as well as antidepressant effects, which is unproved. Droperidol is discussed among the neuroleptics as though it were used as frequently as haloperidol. For these reasons, the information regarding clinically used psychotropic drugs will not be helpful to the practicing psychiatrist but may be useful to the technically minded nonpsychiatric professional.

Despite these concerns, this volume can be recommended as a complete, unbiased, and professional review of psychoactive drugs of abuse. Although technical, it is clearly written, free from jargon, and should serve as an accessible reference for psychiatrists who are unfamiliar with neuropharmacology and with substance abuse.

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Antipsychotics: Drugs in Psychiatry, vol. 3, *edited by Graham D. Burrows, Trevor R. Norman, and Brian Davies. New York, Elsevier, 1985, 267 pp., $72.25.*

This book of 18 chapters is intended for the researcher, the generalist, and the specialist. The chapters are uneven, however. The areas selected are primarily for the clinical investigator, and there is very little coverage of basic research. Since this is a heroic and broad series, *Drugs in Psychiatry,* launched by Dr. G.D. Burrows and his col-

leagues, no doubt the basic research on antipsychotics is located elsewhere in the series. There are only two chapters on basic research in this volume, and these deal with the endocrine and endorphin aspects of neuroleptic action. Since all neuroleptics, with the single exception of reserpine, primarily block dopamine receptors in direct relation to their clinical potency, a chapter on this would have been useful. Thus, the artificial subdivision of antipsychotics into such groups as aliphatic and piperidine and piperazine is rather obsolete. They are all D_2 receptor blockers, and reserpine acts by depleting dopamine. The basic science of side effects, wherein other receptors are blocked, has also been omitted.

Some of the clinical sections have been written by extremely experienced and excellent psychiatrists. Many of the usual questions that hospital residents or less experienced psychiatrists would ask, however, are left unanswered. Although it is placed in the section on basic research, the chapter by T. Van Putten, P. May, and S.R. Marder is most useful clinically.

A third of this book is devoted to the concentrations of antipsychotic drugs in plasma. A major breakthrough remains to be made in this area. Since the concentrations of neuroleptics in the CSF are those which determine the clinical actions, it remains for the basic researchers to provide new and more sensitive tools for routinely measuring the "free" or unbound concentrations of neuroleptic in the plasma *water*. A chapter on this challenge remains to be written.

In summary, this book provides useful reviews on plasma levels, depot neuroleptics, the variety of neuroleptics, tardive dyskinesia, and neuroleptics in children and the elderly as well as adverse effects and drug interactions.

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Behavioral Pharmacology: The Current Status, *edited by Lewis S. Seiden and Robert L. Balster. New York, Alan R. Liss, 1984, 552 pp., $78.00.*

This book represents a laudable attempt to provide a current overview of one of the most explosively growing fields in modern science. The many contributors to this edited volume are all recognized authorities in the field who bring a wide variety of perspectives and approaches to bear on behavioral pharmacology.

Traditionally, of course, the pharmacology of psychoactive compounds has been analyzed from two very different perspectives: biochemical approaches, exemplified by biochemical analyses of drug-induced neurotransmitter or receptor modulation, and behavioral approaches, exemplified by analyses of drug-induced behavioral changes in animals under varying environmental conditions. This latter approach is the one emphasized in the present volume. Unfortunately, much of this work tends to revert to the "black-box" behavioral pharmacology that typified the field in the 1950s and 1960s, when virtually nothing was known of the chemical neuroanatomy or "wet wiring diagram" of the brain. But recent advances in histochemical and immunochemical tracing of CNS circuitry have made it possible to describe psychoactive drug action on defined CNS circuits subserving given behavioral patterns rather than simply describing psychoactive drug action on the two divergent endpoints of biochemistry and behavior. To their credit, some of the authors contributing to this volume do take this approach (particularly in the chapters in the section on Behavioral Pharmacology of Antianxiety and Antipsychotic Agents), but, in my opinion, this volume would be a far stronger contribution to the field had more of its authors adopted similar approaches. Behavior is, after all, as the editors of this volume themselves point out in their preface, the complex physiological response that results from neurochemical and neurophysiological responses occurring in the nervous system. Now that it is becoming possible to define at least some behaviors in terms of the activation of underlying substrate circuitries, it certainly seems that the time has come to begin to define psychoactive drug action in similar terms. From such analysis, it is hoped, may well come not only fundamental new understandings of the appropriate pharmacological groupings of psychoactive agents (including many of the abused substances and behaviorally toxic substances that currently defy adequate categorization) but also fundamental new insights into the specific CNS pathologies that underlie psychiatric illness.

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Endocrine and Metabolic Effects of Lithium, *by John H. Lazarus. New York, Plenum, 1986, 208 pp., $35.00.*

This book is exactly what its title says it is. It is a comprehensive review of the endocrine and metabolic effects of lithium, with detailed references to studies in animals and man. What it is not is a review of the clinical indications of lithium, although this is briefly mentioned in chapter two. The book has an excellent chapter on the history of lithium and a rather brief but well-referenced chapter on clinical indications for lithium therapy. This chapter reviews studies in depression and schizophrenia as well as the use of lithium in children, alcoholism, drug abuse, and nonpsychiatric applications. There is a table noting drug-drug interactions relating to lithium; this is quite brief.

The remainder of the book is concerned with the metabolism of lithium. The chapters are on lithium in the cell, lithium in brain metabolism, thyroid effects of lithium, effect of lithium on carbohydrate metabolism, effect of lithium on the kidney, and other metabolic effects of lithium. Each chapter is exceedingly well referenced, and the references go at least through 1984.

In many ways this book is a delight: it is a truly useful summary and has an adequate list of references for metabolic and endocrine effects of lithium. In other ways, it is disappointing and, I think, will be of limited utility for the clinician. For example, in the paragraph related to lithium effects on the heart, there is a statement that lithium use can be associated with cardiac conduction abnormalities, and there is one reference to a review of this matter. This seems to underplay the role of lithium in sinus node dysfunction. If this area were elaborated on, it would give the book a better clinical flavor. However, this is indeed the disappointment of the book: although well written and well referenced, it is of limited value for clinicians. I suggest that the book would be an excellent addition to the libraries of departments of psychiatry to serve as a reference text for endocrine and metabolic effects of lithium.

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STRESS DISORDERS

Stress, Appraisal, and Coping, *by Richard S. Lazarus and Susan Folkman. New York, Springer Publishing Co., 1984, 445 pp., $31.95.*

Stress Inoculation Training, *by Donald Meichenbaum. New York, Pergamon Press, 1985, 107 pp., $17.50; $9.95 (paper).*

Scientific interests clearly run in cycles. Certain topics become all the vogue and demand considerable attention in the popular and professional literature. Stress is now "in." To quote from the beginning of the Lazarus and Folkman book,

> It is virtually impossible today to read extensively in any of the biological or social sciences without running into the term stress. The concept is extensively discussed in the health care fields, and it is found as well in economics, political science, business and education. At the popular level, we are flooded with messages about how stress can be prevented, managed and even eliminated.

Stress has taken on the dimensions of an all-encompassing intervening variable and an explanatory construct. It is invoked to explain why people become ill, why they die earlier than they need to, why athletes do not perform up to their potential, why employees are not productive, and so on. When a concept gains popularity, it begins to color clinical practice. What people read about tells them in which areas they need assistance from people helpers. As lay people become more sophisticated about the deleterious effects of stress, they require practitioners to become stress management consultants. And so professionals seek out the latest literature and research findings to increase their skill at stress management.

The two books under review are representative of current thinking about stress incorporating the cognitive perspective. Beginning with Beck's work on the treatment of depression with cognitive psychology (1), the treatment approach has continually found additional areas of application.

Scientific thinking has changed considerably since Lazarus's original book was published in 1966 (2). Since then, cognitive approaches to stress have become rather widely accepted. The intent of *Stress, Appraisal, and Coping* is to present in detail Lazarus's theories about stress, appraisal, and coping, drawing heavily on his own research work, and to examine major movements and applications in the field from the perspective of the theoretical approach taken. The authors maintain that this is an idea book, not a review of research per se.

The book proceeds through an orderly and logical developmental process for eight of the 11 chapters, centering on the three concepts mentioned in the title—stress, appraisal, and coping. Two of the later chapters, dealing with emotion and methodological issues, seem less related to the major thrust of the book. Several key themes recur in the authors' very orderly theoretical development of the topics discussed. One is interactional focus. Psychological stress is defined as a particular relationship between the person and the environment. Stress is not seen as a product of either person or environment in isolation. A second theme is the critical nature of cognitive factors and the appraisal process: "It is not change per se that constitutes stress, but rather the way it is appraised and dealt with by the individual." A third theme is that stress cannot be dispensed with or eliminated. Instead, the emphasis is on learning to cope effectively by adaptational activities. I particularly appreciated the authors' nonjudgmental stand that no coping strategy should be labeled good or bad and that there is no one right or proper way to cope. Effective coping is determined by the combination of the person, the situation encountered, the stage of life development, and the effectiveness of the coping process. A fourth theme has to do with the relationship between stress and developmental stages. The authors present the view that what is perceived as stressful depends on the individual's state of life. Underlying all is the consistent theme of individual differences. The authors emphasize again and again that what is perceived as stressful by one individual in one state of life may not be perceived as stressful by another individual in the same state of life.

Given that the book is presented as an idea book, it is appropriate to ask how effective it is in generating ideas. In my opinion, it does a pretty good job. Interesting questions are raised in chapter four about the relationship between temporal factors and stress, particularly duration and temporal uncertainty. There is not much literature available on questions concerning the effects on the stress process of not knowing how long an event is going to last or when it is going to happen. A topic of considerable interest in the current stress literature is the "Type A" behavior pattern. Researchers and clinicians have struggled with the question of how best to modify this behavior pattern. The authors raise interesting questions about the consequences to the individual of modifying this behavior pattern and the sacrifices in personal satisfaction that may be made in the interest of possible greater longevity. In chapter seven the authors discuss the learned helplessness phenomenon. As one might expect, they inject a cognitive perspective, indicating that most of the animal literature from which the learned helplessness concept derived did not consider the cognitive perspective. In addition, they also inject an individual differences perspective, indicating that more than the life history is involved in whether an individual approaches a stressful event with a helpless perspective. In chapter eight some theorizing is presented regarding the relationship between stress and social change.

By way of some summary impressions of the book, I noted that my interest level varied considerably. At times the book seemed positively enchanting; at other times it seemed tedious. The historical focus reviewing changes in theoretical perspective within psychology, for example, moving away from drive reduction theory and motivation, added a refreshing backdrop to current thinking. It is true that the authors explicitly state that the book is not intended to be a comprehensive review of research in the area; instead, research had been selected to support a particular conceptualization. Nevertheless, it is still bothersome that as many as 28 references were made to Lazarus's own research. One nagging doubt that continued to surface had to do with the recency of the literature under review. On an impressionistic basis, it seemed that many of the references dated back 8 years and more. In summary, the book is ambitious, intends to be comprehensive, is addressed to a wide audience of specialty groups, and is deserving of attention by those who are interested in gaining a useful perspective on stress management.

The objects of *Stress Inoculation Training* by Donald Meichenbaum are 1) to "go public" with a particular treatment approach and 2) to influence the internal dialogue of clinicians and researchers interested in stress. The book is reminiscent of an intensive workshop on a specialized topic

area, in this instance, stress inoculation training. As a matter of fact, I am familiar with much of the material from attending a 2-day personal workshop with the author. The theoretical focus is similar to that already described in the Lazarus and Folkman book. (Meichenbaum cites Lazarus and Folkman as a resource several times in his text.)

Stress inoculation training is a generic term referring to a treatment paradigm consisting of a semistructured clinical training regimen. The specific training operations vary, depending on the population treated. Stress inoculation training combines didactic teaching, Socratic discussion, cognitive restructuring, problem solving, relaxation training, behavioral and imaginal rehearsal, self-monitoring, self-instruction, self-reinforcement, and efforts at environmental change. The treatment approach is intended to nurture and develop coping skills ("learned resourcefulness").

Stress inoculation training proceeds in an orderly fashion through three separate phases described as 1) conceptualization, 2) skills acquisition and rehearsal, and 3) application and follow-through. Separate chapters are devoted to explaining what happens in each of these phases.

If the reader is interested in a quickly read "how-to" book detailing the application of cognitive techniques but incorporating other procedures as well to the field of stress management, this little volume fills the bill.

As mentioned in the beginning of this review, one objective of professionals is to become more effective as stress consultants. Meichenbaum emphasizes repeatedly the value of clinical acumen in working as a stress manager with stressed individuals. An appropriate way to close this review is to quote some of Meichenbaum's attempts at modifying the reader's internal dialogue (presented as guidelines and reminders for stress consultants):

1. Be cautious in proposing any specific coping techniques.
2. Be frank, open, and honest with clients in telling them what is and is not known.
3. Enlist clients as collaborators in determining the most useful coping approaches.
4. Be flexible in individually tailoring the coping training regimen to clients' specific situations and capabilities.
5. Adopt an analytic assessment approach to determine what needs to be trained.

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Vietnam Veterans: The Road to Recovery, *by Joel Osler Brende and Erwin Randolph Parson. New York, Plenum, 1985, 270 pp., $17.95.*

More than a dozen books have been published in recent years that focus on the psychosocial consequences of the Vietnam conflict for those who survived as its veterans. This book emerges as among the best. It is well written, inclusive, and useful.

The book is written by two psychotherapists with many years of experience working with troubled Vietnam veterans. Brende, a psychiatrist, and Parson, a psychologist and Vietnam veteran, make a good collaborative effort, producing a book useful to both scholars and clinicians.

It begins with a discussion of the complexities and subterfuges of the Vietnam war—both there and at home. The authors then trace the major difficulties faced by these veterans, particularly those troubled by their war experiences, and the recovery process. There is a good overview of combat-related posttraumatic stress disorder. Moreover, they provide a useful frame of reference for understanding the mental health consequences of the war for its veterans.

What is unique about this book is the extraordinary attention paid to issues rarely addressed in other Vietnam veteran books: family life and interpersonal adjustment, the special problems and circumstances of women and ethnic minorities, and identifying local and regional resources providing readjustment services for Vietnam veterans.

At a time when interest is growing once again to intervene militarily in the politics of another country, the lessons of past interventions should be carefully studied. Among the lessons of this book is that the horror of war continues in the psyches of those who fought it and that the time and cost of purging the painful emotional residue of war are greater than those of the war itself.

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The Trauma of War: Stress and Recovery in Viet Nam Veterans, *edited by Stephen M. Sonnenberg, M.D., Arthur S. Blank, Jr., M.D., and John A. Talbott, M.D. Washington, D.C., American Psychiatric Press, 1985, 444 pp., $24.95.*

On the inside part of this book's jacket we can read that the book is

> a unique psychiatric source book. This volume provides a scientific account of the psychological ravages of the war in Viet Nam on the men and women who served there, but throughout this book reverberate the troubled voices of these veterans—and the sensitive voices of the mental health professionals who have been directly affected by their work with these veterans.

I have to agree in general with this statement, with the exception that I do not believe that this book is unique. It has glimpses of being "the book" but is only one of several volumes written by different health professionals on the subject.

The Trauma of War has solid textbook chapters, such as Arthur L. Arnold's two chapters, "Diagnosis of Post-Traumatic Stress Disorder in Viet Nam Veterans" and "Inpatient Treatment of Viet Nam Veterans With Post-Traumatic Stress Disorder" and Lawrence C. Kolb's "The Place of Narcosynthesis in the Treatment of Chronic and Delayed Stress Reactions of War." It has chapters with a sociological orientation, such as Robert S. Laufer's "War Trauma and Human Development: The Viet Nam Experience," in which he shows his expertise on the subject. It has treatment chapters, uneven in their quality and covering a variety of topics, with emphasis on psychotherapeutic techniques. It has chapters about "minorities" (women, blacks, and Hispanics), which are written with more feeling than accuracy. The one about women, written by Janet Ott, is a

nice, short chapter written by a dedicated clinician/therapist. Dr. Parson's contribution about blacks is "heavy," full of new terms and new concepts that he uses—unsuccessfully—to convince us about how difficult it is to do psychotherapy with black patients. The last of the group, by Gregorio Piña III, is disappointing. Other chapters include one by Harry C. Holloway and Robert J. Ursano and one by Ursano that rank among the best in the book. These chapters discuss "Viet Nam Veterans on Active Duty" and "Viet Nam Era Prisoners of War: Studies of U.S. Air Force Prisoners of War."

In a controversial but well-written chapter Arthur S. Blank, Jr., discusses "The Unconscious Flashback to the War in Viet Nam Veterans: Clinical Mystery, Legal Defense, and Community Problem." Raymond Monsour Scurfield and Blank's contribution "A Guide to Obtaining a Military History From Viet Nam Veterans" is, as the title says, a guide, useful but just a guide. John O. Lipkin, Blank, and Scurfield then discuss the "Forensic Assessment of Post-Traumatic Stress Disorder in Viet Nam Veterans." This chapter has a footnote stating that it was originally published as "Post-Traumatic Stress Disorder in Viet Nam Veterans: Assessment in a Forensic Setting," which more accurately reflects the content of the chapter. It includes, again, such headings as "the history of the PTSD diagnosis," "*DSM-III* and PTSD," "the nature of the Viet Nam war," "making an accurate diagnosis of PTSD," and "the military history"; only at the very end and briefly does it deal with the issues "assessing culpability" and "legal disposition and treatment implications," which the authors fail to develop fully and in more detail.

In summary, this is a good book, with a lot of "editable" material (about 50% of the chapters address repetitiously the issues of diagnosis, *DSM-III,* and the nature of war), uneven in its quality, and sometimes showing more affect than accuracy. I am still waiting for the work that will do justice to the importance of the elusive disorder called posttraumatic stress disorder.

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Reprints of Book Forum reviews are not available.

Letters to the Editor

Human Psychopharmacology

SIR: I should like to draw the attention of your readers to *Human Psychopharmacology: Clinical and Experimental,* a new international journal that was launched by John Wiley & Sons in the autumn of 1986. *Human Psychopharmacology* aims at communicating the results of clinical and experimental studies relevant to the understanding of new and established psychotropic drugs. To this end we will publish papers on experimental human psychopharmacology, volunteer studies, the results of efficacy studies, especially large-scale and placebo-controlled trials, and research findings of the effects of psychotropic drugs (including unwanted effects) on various physiological systems.

We will also publish articles on animal studies, as long as these are relevant to human psychopharmacology and the theoretical background of the work is spelled out in such a way as to give clinicians more insight into work in the laboratory. We see this as an important link between basic scientists and practicing clinicians.

To broaden the scope of the journal, we also expect to publish papers on substance abuse and dependence and on the broader historical, ethical, psychological, and social aspects of psychotropic drug use, misuse, and abuse.

The journal will include reports of original research, including short communications, reviews, and comments by leading authorities (with discussion by other experts), papers on practical therapeutics, reports of international meetings, book reviews, correspondence, and a schedule of forthcoming events. Papers will be strictly refereed, and only studies that meet acceptable ethical standards governing experimentation in animals and human beings will be considered. Proceedings of meetings and symposia that meet strict editorial criteria may be published as supplements to the journal. We aim to publish contributions within 3–6 months of final acceptance.

Anyone interested in further information about *Human Psychopharmacology* should write directly to me.

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Cortisol and Dexamethasone Blood Levels and Phytohemagglutinin Response

SIR: The phytohemagglutinin (PHA) response is the most common measure of immunologic competence that has been studied in relation to various forms of psychopathology. This test measures the extent of the mitotic response of T lymphocytes (in vitro) to phytohemagglutinin, a plant mitogen. The extent of mitosis is reflected in the uptake, from culture, of radioactive thymidine by the stimulated cells, and the results are expressed in counts per minute.

In 1985 we commented in the *Journal* (1) on a study by Lowy and associates (2) in which they had found a reduction in the effects of dexamethasone on PHA stimulation in some depressed subjects. We speculated at the time on the possible role of cortisol in regulating PHA responsiveness. We have since studied the relationship between cortisol and dexamethasone concentrations in the blood and the PHA response in normal subjects.

For four normal subjects, cortisol and dexamethasone concentrations were assayed in blood drawn at 8:00 a.m. and 4:00 p.m. on 3 consecutive days. At 11:00 p.m. of day 1, each subject received 1 mg of dexamethasone. Lymphocytes from a portion of each sample were stimulated with PHA, and T cell subpopulations were determined by means of fluorescent-labeled monoclonal antibodies in a flow cytometer.

No significant relationship was found between cortisol level and PHA response either before or after dexamethasone (for all samples, $r=-.43$, $p=.13$). There was, however, a significant negative correlation between dexamethasone concentration and PHA response ($r=-.63$, $p=.05$). Lymphocyte subpopulations were not significantly correlated with the concentrations of either cortisol or dexamethasone.

These findings provide empirical support for our earlier speculation that, in the physiological range, cortisol does not play a major role in influencing the PHA response. On the other hand, dexamethasone, a potent exogenous steroid, does appear to suppress PHA response in a dose-dependent fashion.

We would like to point out that PHA response represents only one of many aspects of immunologic competence and that glucocorticoids and others do affect other arms of the immune response such as the production of interleukin-1 (3). It would be advisable in future studies to include a more complete profile of immunologic functions.

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"Simple Dissociative Disorder": A Subcategory in *DSM-III-R?*

SIR: *DSM-III* is being used in research and training as well as in clinical work in a large part of the Third World, including India. However, there are many weaknesses and

shortcomings of *DSM-III* as seen from the Third World perspective (1).

I wish to share with colleagues one such shortcoming observed in a recent study (2) of the application of *DSM-III* to Indian patients diagnosed as having hysteria by *ICD-9* criteria. By far the most common dissociative state encountered was in the form of recurrent, short periods of dissociation, lasting a few minutes to a few hours, with sudden onset and termination. During this period the person remains relatively unresponsive to the environment and even to painful stimuli. This state is usually, but not always, associated with stress, which may be in the form of sudden emotional trauma or relatively longer lasting stressful situations. During the dissociative state, the person is usually mute but in some cases may cry, shout, or verbalize thoughts that are completely at variance with his or her usual personality. There may also be accompanying motor movements that either resemble generalized epileptic convulsions or are bizarre; these states are commonly but loosely referred to as hysterical seizures. After recovery the person's conscious memory for the period of dissociation is either absent or patchy; however, memory for events before the onset of dissociation and personal identity are well preserved.

Patients presenting with these dissociative states as their sole or predominant symptom cannot be categorized under any of the existing specific subcategories of dissociative disorders in *DSM-III* (psychogenic amnesia, psychogenic fugue, multiple personality, and depersonalization disorder). Presently, these patients have to be assigned to the subcategory of atypical dissociative disorder. This arrangement becomes highly unsatisfactory to psychiatrists working in regions where these brief dissociative states, unaccompanied by other psychiatric symptoms, are encountered frequently. In Western countries these states may be much rarer, but I believe they are not entirely absent.

I suggest that an additional subcategory of "simple dissociative disorder" be introduced in the dissociative disorders category of *DSM-III-R,* with the following criteria:

1. Short periods (a few minutes to a few hours) of alteration in consciousness manifested by relative unresponsiveness to external environment and painful stimuli;
2. Sudden onset and termination;
3. After termination of the episode, partial or complete amnesia for events that occurred during the period of alteration in consciousness;
4. Disturbance is not due to an organic mental disorder;
5. Associated features: motor movements of the body that may resemble generalized epileptic convulsions or may be bizarre; crying, shouting, or verbalizing thoughts that may be completely at variance with the usual characteristics of the person's personality; and possession states.

These criteria obviously may have to be modified in view of the clinical experience of psychiatrists from other countries and according to the results of systematic field trials.

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The Cortisol Suppression Index and the DST

SIR: Bernstein and Chung (1) proposed the cortisol suppression index (CSI) as an alternative to the dexamethasone suppression test (DST) in the investigation of hypothalamic-pituitary-adrenal dysfunction in depression. The CSI is the ratio of the predexamethasone to the postdexamethasone cortisol level, measured at the same time on consecutive days. The authors suggested that an 8:00 a.m. CSI of less than 7 and a 4:00 p.m. index of less than 2.5 indicates DST nonsuppression. We have recently examined the CSI in relation to the DST in nine patients with anorexia nervosa, seven age-matched control subjects, and 28 patients with dementia. The criterion for DST nonsuppression was a postdexamethasone cortisol concentration of 50 ng/ml or more, determined by comparison with DST results in normal control subjects (2, 3).

There was good correspondence between the two indexes for anorexic patients and control subjects; only two anorexic patients who were DST nonsuppressors were misclassified as CSI suppressors (the 9:00 a.m. CSI ratios were 7.5 and 9.1), and one control subject who was a DST suppressor was misclassified as a CSI nonsuppressor (the 9:00 a.m. CSI ratio was 6.5). For the demented patients, however, there was a nearly exact correspondence between the DST and CSI results. Only one of 15 DST nonsuppressors was misclassified as a CSI suppressor (the 4:00 p.m. CSI ratio was 2.9). All 13 DST suppressors were also suppressors according to the CSI.

These findings support the aforementioned conclusion that the CSI is an alternative measure to the DST. However, its value in relation to the DST has been disputed for the diagnosis of depression (4), and its prognostic value remains to be investigated.

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Panic Disorder in Prepubertal Children

SIR: According to an epidemiological study of adults (1), the onset of panic disorder peaks between the ages of 15 and 19 years, and about 18% of cases begin before age 10. Despite this retrospectively documented early onset, almost all the literature on panic disorder is about adults. We are aware of one case report of panic attacks in two prepubertal children (2).

This is the first report, to our knowledge, of cases in which a structured psychiatric interview (the Diagnostic Interview for Children and Adolescents) (3) and an echocardiographic evaluation were done for two prepubertal boys, 10 and 8 years old, who met *DSM-III* criteria for panic disorder. They

were among the 11 patients, ages 5–13 years (out of 95 inpatients and 143 outpatients), referred for separation anxiety with school phobia during the past 12 months. The younger child was an inpatient. They presented with recurrent, severe, nonsituational, spontaneous anxiety attacks, with dyspnea, palpitations, chest pain, paresthesias, and trembling. These episodes occurred more than once a week and lasted about 15–20 minutes. The parent of one of the children reported that the child had had recurrent severe anxiety episodes since infancy. In the other patient, the onset was at age 5 years. Both boys developed secondary school phobia and agoraphobia, with complete inability to attend school or leave home alone. The IQs of both were above average. Results of laboratory tests, including thyroid function, were normal. They were not using adrenergic drugs. The younger patient was enuretic and encopretic. Both the patients had an echocardiogram, and one showed mitral valve prolapse.

Panic disorder had been present for at least three generations in these families. Only one parent's family was affected—consistently with single-gene transmission (4). One patient's paternal grandmother and paternal aunt had panic disorder; his father was apparently normal. This suggests an autosomal dominant transmission with incomplete penetrance.

We conclude that panic disorder can be diagnosed in a prepubertal child by using the *DSM-III* criteria for adults. The relationship between childhood separation anxiety/school phobia and later adult panic disorder is known (5). Children with severe school phobia should be interviewed, using age-appropriate vocabulary, to look for symptoms of adult-type primary panic disorder antedating the phobic avoidance. Thus, the currently used diagnoses of "school phobia," "separation anxiety," and "overanxious disorder" may be partially replaced by highly validated adult criteria for panic disorder. As in adults, mitral valve prolapse should be suspected in these children.

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Use of Tricyclic Antidepressants in a Patient With Malignant Hyperthermia

SIR: Malignant hyperthermia is a rare hypermetabolic disease state characterized by a fulminant rise in temperature in susceptible individuals (1). Definitive diagnosis of malignant hyperthermia is based on an in vitro halothane/caffeine-induced contracture test of muscle biopsy specimens (1, 2). Malignant hyperthermia is most commonly triggered by exposure to inhalational anesthetics or muscle relaxants such as succinylcholine (1–3). It has also been said to occur with the use of psychotropic drugs such as haloperidol, monoamine oxidase inhibitors, diazepam, and tricyclic antidepressants (2, 3). Although tricyclic antidepressants have been implicated as precipitants of malignant hyperthermia, we are not aware of any clearly documented case reports. We report here the case of a patient with biopsy-proven malignant hyperthermia who was treated with three different heterocyclic antidepressant agents.

Ms. A, a 34-year-old white married woman with well-documented malignant hyperthermia, was hospitalized for treatment of severe depression. Her affective disorder had persisted for 18 months and was manifested by dysthymia, insomnia, anorexia with associated weight loss, fatigue, poor concentration, and persistent suicidal ideation. She was treated initially with trimipramine, a predominantly serotonergic agent, at doses up to 250 mg/day for a period of 4 weeks, with careful monitoring of vital signs. As she had no therapeutic response to this drug, her treatment was changed to desipramine, a relatively selective noradrenergic agent, in doses up to 200 mg/day. A good therapeutic response was obtained after 2 weeks; however, Ms. A developed an allergic skin reaction, which made it necessary to discontinue the drug. She was then treated with maprotiline, a tetracyclic compound structurally related to the tricyclics that is also a relatively selective noradrenergic agent, at doses up to 150 mg/day, with no difficulty encountered after 2 weeks.

This case illustrates the successful sequential use of three tricyclic antidepressants in a patient with proven malignant hyperthermia. Despite suggestions in the literature that tricyclic antidepressants may be potential triggers of malignant hyperthermia reactions, we encountered no difficulties even with the use of three such agents. Although limited conclusions can be drawn from a single case, our experience with this patient suggests that tricyclic antidepressants can be safely used in patients with malignant hyperthermia.

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Treatment of a Patient With an Airplane Phobia

SIR: Mr. A, a 70-year-old self-employed man, developed a panic reaction that prevented his flying in a small commuter plane to his favorite country place. His referring internist, stating that the patient had recently had coronary bypass surgery and had had severe urinary retention, requested that I not prescribe antidepressants for him—even the so-called "nonanticholinergic" ones. Exploration with the patient revealed that he had an intense need to regain control of the

situation. One fear was that when he sat at the back of the plane, he would have to wait for others to get off first. Capitalizing on the patient's sense of humor, I was able to relate this to his frequent, more mundane fear that he would not be the first to get out of a market investment. He also had a claustrophobic sense of helpless suffocation, which was linked to the fact that the air conditioning was not working in the plane the first time the symptom had appeared; the patient had been reminded that following anesthesia for the bypass, he had also had a sense of respiratory paralysis. Mr. A was strongly motivated to get over his symptom in time for a transatlantic flight a month later.

Therapeutic interventions included reassurances that he would not die in panic or "go crazy and start beating the side of the plane" and that the goal was for him to be relaxed rather than to endure flying in a frantic state. I reactivated an old sleeping pill prescription of his for half a tablet of meprobamate for him to take before boarding the plane. The fear of suffocation was approached as irrational in the first place but amenable to suggestion. Instead of inhaling fresh air or oxygen (reminiscent of hospitals), he could carry a nasal spray. Even less obvious to others, he could place strongly flavored peppermint lozenges on his tongue to create a sensation of cool inhalation.

The issue of control was most directly approached, however, when Mr. A himself thought of taking control of the commuter jet. He hired it for himself alone, and at his command the pilot waited, took off, flew around the airport pattern, and landed again and again. Satisfied that he had regained full control, the patient was able once more to take the regular commuter flight. Subsequently, he took a larger shuttle in the northeast corridor and eventually took the transoceanic flight. The case serves to remind us that power issues are important in phobic panic and that phobic desensitization also involves taking charge.

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Anorgasmia Caused by an MAOI

SIR: Cases of female anorgasmia caused by monoamine oxidase inhibitors (MAOIs) were reported in this journal in three separate letters published in 1983 (1–3); a literature search revealed only one subsequent published paper (4) on this topic. In order to augment the sparse literature, I would like to describe an additional case.

Ms. A, a 36-year-old woman with a long history of obsessive-compulsive disorder, which had been refractory to drug (although MAOIs were not tried), behavioral, and traditional psychotherapeutic approaches, was admitted to the inpatient psychiatric service following a suicide attempt with an overdose of imipramine. The patient's depression and obsessions, but not her compulsive handwashing, responded to phenelzine, 60 mg/day.

Three weeks after discharge (after 5½ weeks of taking phenelzine at that dose), Ms. A complained of anorgasmia. This problem was initially thought to be psychogenic in origin, secondary to severe marital stressors, but over the next 6 weeks, Ms. A, who had never previously failed to achieve an orgasm during masturbation, was unable to experience such an event. Then, as the phenelzine dose was reduced from 60 mg to 45 mg/day, her sexual functioning was rapidly restored, even with a concurrent worsening of the marital discord.

Ms. A is the only female patient taking MAOIs under my care who has reported this phenomenon. However, it is important to note that she offered this information freely; she was never specifically queried on the topic of anorgasmia. In fact, a review of the literature reveals that probably all cases of female anorgasmia associated with MAOIs were serendipitously mentioned by the patient. This observation certainly leads to speculation concerning the true prevalence of this infrequently reported phenomenon.

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JAMES N. JACOBSON, M.D.
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Schizophrenia, Panic Anxiety, and Alprazolam

SIR: Several studies have reported that adjunctive treatment with alprazolam improves negative and positive schizophrenic symptoms in some patients (1, 2). Which patients will benefit and how alprazolam works are not known. We have prescribed alprazolam for eight patients with a *DSM-III* diagnosis of schizophrenia and panic attacks, and they have apparently benefited from it. We present one case as an example.

Mr. A, a 26-year-old man with an 11-year history of psychosis, limited social function, and chronic hospitalization, had hallucinations and delusions that improved when he took antipsychotics. However, his discharge from the hospital was prevented by his disorganization, incoherence, and hostility.

Three years ago, he was rehospitalized after escaping to another state. On admission, he thought that blacks were plotting against him and that he engaged in "telepathic communication." On a regimen of haloperidol, 40 mg/day, his agitation and delusions improved, but he remained disorganized, asocial, unmotivated, and irritable. He did not improve further when the dose was changed to haloperidol, 100 mg/day, or when he was switched to thiothixene, 30 mg/day.

Following a chance remark about chest pain, Mr. A was interviewed for a history of panic attacks. He described episodes of panic with abrupt onset, chest pain, palpitations, dyspnea, dizziness, and fears of dying or losing control that had occurred at least daily since he was 5 years old.

Alprazolam, 0.25 mg t.i.d., stopped his panic attacks within a week, and he became less fearful of black patients. Within 4 weeks, he felt "mentally stronger . . . enthusiastic . . . able to enjoy life." He enjoyed listening to a new radio and reading and noted alleviation of paranoid fears. He felt that he was more likable but also that he was "on trial for feeling normal." In the next 12 weeks Mr. A had occasional angry outbursts and a few more panic attacks. His dose of alprazolam was gradually raised to 1

mg q.i.d., and the panic attacks ceased. He became more socially related, humorous, and engaging and talked coherently of discharge plans. Improvement persisted 20 weeks after alprazolam was started. He was successfully discharged to a rehabilitation program.

Our eight cases indicate the possible value of adjunctive alprazolam in treating schizophrenia with panic attacks. All patients ceased having panic attacks and showed improvement in both positive and negative schizophrenic symptoms. Consistent with findings in previous reports (3), we found that antipsychotics alone did not benefit and may have exacerbated panic.

Surprisingly, schizophrenic symptoms and panic often improved together. Adjunctive alprazolam may benefit panic (4) and negative symptoms due to severe anxious inhibition and social avoidance. Panic might also contribute to episodic agitation and disordered thought. Conceivably, panic could exacerbate or even precipitate psychosis. Some patients reported panic attacks preceding their initial psychosis.

Elicitation of panic history is impaired by the patient's psychosis and reluctance to describe panic attacks. One patient feared that describing panic would provoke an attack. History-taking is aided by inpatient observation and family interviews.

One potential problem is that alprazolam treatment may lead to uninhibited, hostile, or impulsive behavior (5). Although substantial cognitive pathology remains even after marked pharmacologic response, improved relatedness may help some patients benefit from psychosocial treatment. Definitive controlled studies are needed to evaluate alprazolam as an adjunctive treatment for schizophrenia and to assess the value of panic attacks for predicting therapeutic benefit.

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More on *The Ego Ideal*

SIR: In a book review of *The Ego Ideal: A Psychoanalytic Essay on the Malady of the Ideal* by Mme. Janine Chasseguet-Smirgel, published in this journal (1), Dr. George Pollock concluded his positive assessment with the suggestion that "the clinician as well as the political scientist and philosopher will find much to think about in this relatively modest-sized monograph." In addition, he correctly noted the relationship of shame to the ego ideal, a point that I have also considered (2).

However, I wish to suggest several additions to Dr. Pollock's rather general comments. Earlier, he had indicated that "the reminder that man can live by ideals, values, cooperation, and positive goals is one that is sorely needed." In exclusively emphasizing the positive and "loving" (3) aspects of the ego ideal, Dr. Pollock, I believe, has failed to consider what may be the most original contribution of Chasseguet-Smirgel's book, embodied in the book's subtitle, which emphasizes the *malady* of the ideal. The author expounds a view that man is perpetually driven to attain the ideal of re-fusion with that state of narcissistic omnipotence and perfection from which he was inalterably separated at the point of first recognizing the existence of the "not me." According to Mme. Chasseguet-Smirgel, "This seems to be the crucial moment when the narcissistic omnipotence that he is forced to give up is projected onto the object, the infant's first ego ideal, a narcissistic omnipotence from which he is henceforth divided by a gulf that he will spend the rest of his life trying to bridge" (p. 6). The driven quest, and inevitable failure, to attain fusion with the ideal is the source of the utter depletion and devastating shame that may lead to the "guiltless despair" and even suicide of later life—"the wish to wipe out the unbearable sense of mortification and nameless shame imposed by the ultimate recognition of a failure of all-encompassing magnitude" (4, p. 241).

I also differ with the implication in Dr. Pollock's review that this "modest-sized monograph" may also be of modest importance. I believe that the ego ideal, and the malady and shame which it inevitably engenders, is the centerpiece of the disorders of narcissism that are so prominent in our clinical work. Thus, the book under consideration is, for the reasons noted by Dr. Pollock, a work of critical importance to the clinician who endeavors to grapple with his or her patients' narcissistic maladies.

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ANDREW P. MORRISON, M.D.
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More on the Globus Hystericus Syndrome

SIR: I am prompted to write by the recent report on the prevalence and treatment of the globus hystericus syndrome by Susan R. Brown, M.D., et al. (1). I have seen a number of such cases and would like to describe one of them.

Ms. A, a 34-year-old married woman, presented with symptoms of tightness in the throat, which resulted in difficulty in eating and drinking because she feared that she would choke. These symptoms had appeared several

months after she gave birth to dizygotic twins. Associated symptoms included tachycardia, palpitations, lethargy, irritability, poor concentration, initial insomnia, and early morning wakening. Ms. A was given a diagnosis of a conversion disorder related to an anniversary phenomenon (her mother had died 1 year earlier). No physical cause for the symptoms was found. Initially, a psychotherapeutic approach was followed, but without success. Ms. A was later started on therapeutic doses of imipramine, and after a fortnight she recovered fully. It was later discovered that there was a family history of endogenous depression.

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SIR: I am writing with reference to the recent article on the globus hystericus syndrome. I recently treated a 58-year-old woman who had had marked globus hystericus for approximately 4 months. She had been treated with steroids by an ear, nose, and throat specialist and with biofeedback by another physician before coming to me. Neither treatment had done any good. She had become anxious and tearful, with insomnia and other depressive symptoms as well as phobic symptoms. Conceptualizing her globus hystericus as primarily an anxiety symptom with an associated depressive syndrome, I treated her with imipramine, 150 mg/day. Her previously unresponsive symptoms cleared in just over 2 weeks.

In this case, as in some of the cases described by Dr. Brown et al. in their article, although there was an associated depressive syndrome, the globus hystericus predated the depression syndrome by some time. I would agree that antidepressants are clearly worth a trial in patients with globus hystericus.

SAUL H. ROSENTHAL, M.D.
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SIR: The article on the globus hystericus syndrome reminded me of my own theory about globus hystericus. I have had many depressed patients spontaneously tell me, "I have this lump in my throat and I'm afraid I will choke," or words to that effect. Although this is not their chief complaint, they are genuinely anxious (as one would expect) about this symptom, and usually it is volunteered in the first interview. Empirically, I have learned to respond in the following way.

First I will ask, "Have you felt like crying lately?" The usual reply is, "Yes, but I can't" or "I cry all the time and for no reason." I reply that I think the "lump" is the type of lump we get in our throats before we begin to cry. After a period of thought, the patient will say, "Gee, I never thought of that," and a look of relief appears on his or her face. I then tell patients who cannot cry that they might feel better if they could somehow permit themselves to cry. To both kinds of patients I indicate that I think the lump will gradually diminish as their feelings of anxiety and depression improve. Patients usually leave the office feeling that they have finally found a theory about their symptom that they can understand, as well as some hope of relief.

I have used the same approach with several patients who had the lump as their chief complaint and for whom globus hystericus was the primary diagnosis. These patients were also depressed enough to warrant treatment. In summary, all of these patients received antidepressant medication and psychotherapy. In all cases the lump improved, at least to the point where it was no longer a significant problem to the patient. I realize that the majority of my patients were depressed, and the few with globus hystericus were probably not the most severe cases. I also note that the relief obtained by Dr. Brown and associates' patients was not linked to the remission of their depression. Be that as it may, I can't help thinking that crying or the inability to cry is, at least for some patients, a major etiological factor in their globus hystericus. I wonder whether some of the abnormal esophageal findings in these patients are not also related to crying or the lack of it. In the literature I have read, I do not recall any mention of crying as a factor in globus hystericus. In future studies of such patients, perhaps we could learn something if we more systematically investigated this aspect of their behavior.

FRED WEINSTEIN, M.D.
Columbia, S.C.

Dr. Jenike and Associates Reply

SIR: Dr. Weinstein's clinical observations are worthy of note and warrant further study.

It appears that our patients were somewhat sicker, and they were in fact quite disabled by their symptoms. We believe that the patients were able to cry, but we did not specifically address this issue in psychotherapy. In addition, none of us gets a lump in the throat when we begin to cry, and we do not believe that this is a common experience. Nonetheless, there is nothing to lose by trying Dr. Weinstein's technique, and we appreciate his observations.

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SUSAN R. BROWN, M.D.
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Boston, Mass.

Psychiatrist-Patient Sexual Contact

SIR: The article by Nanette Gartrell, M.D., and associates (1) on psychiatrist-patient sexual contact and the accompanying editorial by William L. Webb, Jr., M.D. (2), chairman of the APA Ethics Committee, addressed the serious problem of sexual misconduct by therapists. When discussing remedies, both papers focused on increasing education (in residency and continuing education) and encouraging colleagues who have sexually acted out with patients to seek professional consultation. These recommendations do not go far enough. Upon learning of a colleague's unethical practice, psychiatrists and other mental health professionals usually have an ethical *obligation* to report sexual and other serious misconduct (3). This obligation is not an absolute one and must be weighed against other ethical principles, including the patient's confidentiality and autonomy. Professionals, however, are reluctant to report for many reasons, and they tend to rationalize away this obligation. Given Dr. Gartrell and associates' findings that most offending psychiatrists had distorted views of sexual contact with patients and that a minority sought consultation on their own, more education and encouragement to seek consultation will be inadequate

interventions. *The Principles of Medical Ethics With Annotations Especially Applicable to Psychiatry,* published by APA, should be amended to *require* psychiatrists to report serious unethical conduct by other psychiatrists if the patients also consent to the reporting. We cannot effectively protect patients and our profession or help the impaired practitioner unless we accept our moral duty to intervene.

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JAMES L. LEVENSON, M.D.
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Dr. Gartrell and Associates Reply

SIR: We strongly agree with Dr. Levenson that the APA code of ethics should be amended to require psychiatrists to report sexual misconduct by colleagues. We found in our survey that very few psychiatrists had ever reported their colleagues for known sexual violations. Our data on psychiatrists' reporting practices and our recommendations for improving reporting and disciplinary procedures will be published in the third paper in our series.

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Clonidine in Benzodiazepine Withdrawal

SIR: I read with interest the report of Wayne K. Goodman, M.D., et al. (1) on clonidine's ineffectiveness in treating benzodiazepine withdrawal symptoms. I wonder whether their data justified their conclusions, since a close look at figures 1, 2, and 3 shows a downward trend in abstinence symptoms beginning 4–7 days after institution of treatment with clonidine. While the authors themselves pointed out this change, they suggested that it corresponded to the expected course of benzodiazepine withdrawal. Both of the previous studies of the natural course of "untreated" benzodiazepine withdrawal that the authors cited in support of this suggestion actually involved reinstitution of benzodiazepines to treat the withdrawal symptoms (2, 3). Follow-up studies of benzodiazepine withdrawal syndromes have revealed the protracted nature of the symptoms; in most patients they last up to 4–6 months after withdrawal (4). Thus, the brief course of symptoms in the authors' cases may reflect either the mild nature of the withdrawal syndrome or, indeed, some therapeutic effect of clonidine. A comparable group of patients treated with placebo during withdrawal may shed some light on this question. The fact that the symptoms declined several days after the beginning of clonidine treatment is not incompatible with a therapeutic effect. In fact, the antianxiety effect of clonidine is reported to become important only during the second week of treatment (5).

An alternative approach to treatment of benzodiazepine withdrawal syndrome may be to begin clonidine treatment before discontinuation of benzodiazepines. A colleague and I have described a patient for whom such a strategy prevented the occurrence of withdrawal symptoms (6). The abstinence symptoms promptly recurred when clonidine was discontinued. We have seen in three other cases in which a similar strategy was used that clonidine has moderate beneficial effect on benzodiazepine withdrawal symptoms, although not all symptoms improve (Keshavan et al., unpublished manuscript).

Clearly, as the authors admitted, more studies are needed before we can proclaim that clonidine is ineffective in treating benzodiazepine withdrawal. While I agree with the authors that other mechanisms such as changes in γ-aminobutyric acid–benzodiazepine receptor complexes may underlie this syndrome, we cannot exclude noradrenergic mechanisms as the basis for at least some of the symptoms.

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Potentiation of Antidepressants by T_3 and Lithium

SIR: James C. Garbutt, M.D., and associates (1) published a paper in which they reported on lithium potentiation of tricyclic antidepressants in patients considered to be refractory to T_3 potentiation. In the four cases they reported, however, the T_3 was added after only 2½ or 3 weeks of tricyclic antidepressant treatment (4½ weeks in one case). Although the authors concluded that these patients were refractory to T_3, we suggest that their failure to respond to T_3 may merely have reflected an inadequate duration of treatment with the tricyclic. Quitkin et al. (2, 3) reported that response to tricyclic antidepressants may take as long as 6 weeks and presented data suggesting that a shorter period of treatment is an inadequate trial of an antidepressant. The effect of time makes it impossible to draw conclusions about these patients' failure to respond to potentiation with T_3. It would be more correct to consider the authors' results a confirmation of the finding of de Montigny et al. (4) that lithium may potentiate the response to tricyclic antidepressants. There remains a need for systematic study of patients refractory to tricyclic antidepressants to demonstrate wheth-

er there is a differential response to potentiation with T_3 or lithium.

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JONATHAN W. STEWART, M.D.
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Dr. Garbutt and Associates Reply

SIR: Drs. Harrison and Stewart have raised an important point concerning duration of antidepressant treatment in their comment on our recent article. Overall, we would agree that a vigorous trial of a tricyclic antidepressant may take as long as 6 weeks. However, several points should be noted.

First, in the article by Quitkin et al. suggesting that a 6-week trial is superior to a 4-week trial (reference 1 in Harrison and Stewart's letter), the patients reported on were mildly depressed (Hamilton Rating Scale for Depression scores for 21 items, <18). Our patients were severely depressed (Hamilton scores for 17 items, >25). Quitkin et al. commented, "We believe a more severely ill patient sample ... would more likely show drug-placebo differences by 4 weeks." In fact, *improvement* with tricyclics is frequently noted within 2–3 weeks (1). In our patients, no improvement was noted after 2½–4½ weeks, which prompted us to initiate treatment with T_3. Furthermore, when the time they were taking a tricyclic and the time they were taking T_3 are combined, our patients were treated for 5½, 4, 5, and 4 weeks, but they still showed no improvement. These results should be compared with those in the study by de Montigny, in which, after 3 weeks of tricyclic treatment, lithium was added and rapid improvement occurred. Therefore, we believe our observation is valid for seriously depressed patients. In fact, we have observed lithium response after lack of T_3 response on several other occasions since the report.

We do believe that further investigation is warranted to compare a longer tricyclic trial with the addition of potentiators such as T_3 and lithium. Heninger et al. (2) did just such a study with lithium and found that continuing antidepressants for an additional 2 weeks was markedly inferior to adding lithium after 3 weeks of antidepressants. To our knowledge, similar data for T_3 are lacking. Random assignment of tricyclic-refractory patients to lithium or T_3 followed by a crossover in nonresponders is still needed to truly assess the differential response to T_3 and lithium.

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Mortality in Neuroleptic Malignant Syndrome

SIR: The paper "Neuroleptic Malignant Syndrome" by James L. Levenson, M.D., (1) mentioned a mortality rate of 20% for this disorder, as attributed to Caroff (2) and Itoh et al. (3). However, a careful look at the paper by Itoh et al. reveals that four patients of a total of 14 died. This gives a mortality rate of approximately 29%, rather than the 20% that was cited.

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The Soviet View of Paranoid Disorder

SIR: The review of recent Soviet literature on paranoid disorder by D.W. and D.K. Swanson (1) should reflect faithfully the phenomenology, treatment, and so forth of this disorder in the Soviet Union. There is, however, some doubt in my mind, since in the section Historical Considerations the Swansons presented the behaviorist simplification and distortion of Pavlov's work. They would make Pavlov look like a rather simple-minded person (similar tendencies exist in Russia with regard to Freud) and discredit his theories more than time and new experience would anyway.

To begin with, Sechenov emphasized the great importance of the somatocerebral afferent connections and hypothesized that stimulation arising from the internal organs (called "dark feelings"), while not becoming conscious, influenced "higher nervous activities." These theories led later to the experimental validation of interoception by the Bikov school. This is exactly the opposite of the Swansons' statement that Sechenov "maintained that psychic activity depended entirely on external stimuli." Again, in opposition to the Swansons' and behaviorists' assumption, Pavlov considered the conditioned reflex as a tool, a probe to examine higher cerebral processes such as irradiation and concentration of excitation and active and passive inhibition. Pavlov did not believe that these were elaborations of simple conditioned reflexes, as the Swansons would have us believe.

Pavlov's thinking on paranoid conditions, which was based on animal experiments and was never tested on humans, was summarized by Ivanov-Smolensky (2): "Paranoiac delusion is explained by phenomena of pathological inertness of excitation with a steady diminution of inhibitory corrections (internal active inhibitions)." Pavlov (3) said,

"There sets in the absolute power of an idea, which not through active inhibition on the basis of other associations, other signals, signals of reality, but through passive inhibition through a process of negative induction, excludes everything not in keeping with it and turns into a fantastic idea of imaginary grandeur, imaginary success."

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LESLIE SOLYOM, M.D., F.R.C.P.(C), M.R.C.PSYCH.
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Dr. Swanson Replies

SIR: Professor Solyom's comments are useful but condescending. He implies that our review of the Russian literature on paranoid disorders may have been flawed by lack of accuracy or by theoretical bias or both. This interpretation is apparently based on disagreement with the brief historical summary of the contributions of Sechenov and Pavlov. I will reply, since my coauthor and translator is currently doing research in the U.S.S.R.

The material on Sechenov and Pavlov was not translated from Russian, as is documented in references 2–5 of our paper (references 1–4 in this reply). The articles we reviewed from the current literature were. Professor Solyom's comments and references suggest that he is knowledgeable in this area of Soviet science and has also read the scientific reports in Russian.

If our historical review attributed to Sechenov and Pavlov an erroneous or excessive modifying influence on the "classic" approach, I regret this. It was intended to demonstrate how their formulations offered some alternative. Furthermore, our comments did come directly from the references cited.

Certainly, Sechenov emphasized the role of stimuli from within the body. But a passage from his *The Reflexes of the Brain* states:

> All psychic acts which occur along reflex lines must be studied entirely physiologically because *their beginning, the sensory stimulus,* and their end, the motor actions are physiological phenomena. Moreover, even the middle, or psychic, element is also strictly speaking often, if not always, not an independent phenomenon—as was formerly believed—but an integral part of this whole process. (2, italics added)

This statement indicates a role for the external stimulus, and the authors of this summary concluded that Sechenov thought that psychic activity depended entirely on the external stimulus (2, p. 156).

Like Professor Solyom, I am aware that Pavlov was an octogenarian when he theorized about the relationship of his laboratory findings to clinical problems. Gantt et al. (3, pp. 48, 49) reported that when Pavlov considered the psychiatric patient, he emphasized the unique contribution of the language function—the second signaling system. Language *represented a higher order of conditioned reflex;* words became the signals of primary signals.

Retterstöl (1, p. 25) noted that Pavlov's conclusions regarding paranoid conditions were attributed to a disturbance in transmission of impulses from the first system to the second. The paranoid person's perception plays a role but has changed meaning because of a morbid tendency to expound.

The paranoid disorders are a heterogeneous group of conditions, ill understood. Summary of the findings of others is difficult in any language; translation complicates the situation.

For whoever might be interested: 1) there is an error in a reference citation (reference 36 on page 828 should be 38), 2) I don't consider Pavlov simple-minded, and 3) I've been called a lot of things, but never a behaviorist.

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DAVID W. SWANSON, M.D.
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Denial in Recipients of Heart Transplants

SIR: I read with interest the article "Graft and Donor Denial in Heart Transplant Recipients" by François M. Mai, M.D. (1), in which he referred to the sparseness of the psychiatric literature on heart transplants, due to "the newness of the procedure." Dr. Mai may not be aware that there is an early psychiatric literature on heart transplants that dates back to the late 1960s and early 1970s, soon after Christiaan Barnard's epochal experiment. For reasons of space, only part of that literature can be cited here (2–6).

The issue of denial (2–5) was noted at that time, as well as a range of other problems, including that of postoperative psychosis (2, 5, 6), an occurrence that was not uncommon then. Denial appeared to be directed not so much at the graft or the donor—some patients voiced intense and complex fantasies about both graft and donor (2, 5)—but at the experience of undergoing a surgical procedure that was still experimental and might have a very poor outcome. Some of us who had the opportunity to care for these patients wondered about this attitude (2–5). It seemed that their posture toward the operation was distinctly counterphobic and that they appeared to dread a "natural" exit from life. The counterphobic attitude toward the operation often seemed to be reinforced by the patient's spouse and family. These issues may be less prominent today, because, almost 2 decades later, the statistics for survival after heart transplant have improved dramatically. On the other hand, they may still be relevant to patients who undergo an artificial heart implant. Here, so far, the outcome has been poor and the risk great.

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PIETRO CASTELNUOVO-TEDESCO, M.D.
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Dr. Mai Replies

SIR: I am familiar with Dr. Castelnuovo-Tedesco's early work in this field and also with the work of Christopherson and Lunde. The latter two authors are cited in my paper "Psychiatric Aspects of Heart Transplantation" (1), which is listed as a reference in my paper on graft and donor denial.

Dr. Castelnuovo-Tedesco's writings and the paper by Kraft that he cites in his reference 5 do refer to denial, but the case material is anecdotal and the patients were a selected rather than a random or consecutive sample. In Dr. Castelnuovo-Tedesco's single case study (reference 2 in his letter), insufficient clinical history was provided to ascertain the reason for concluding that the patient exhibited "massive denial." Furthermore, it is clear from the history that the patient did not express denial toward the donor, because he was described as expressing great interest in the donor, and no mention was made of his reaction to the graft.

In my paper, denial was defined and the clinical data base was described. The material was distinctive, also, in that the subjects were essentially a consecutive sample, and thus it was possible to draw conclusions about the prevalence and character of denial in the total transplant group. I feel that it is important to follow these methodological principles in clinical papers.

I am grateful to Dr. Castelnuovo-Tedesco for drawing attention to early work in this field.

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Co-Occurrence of Schizophrenia and Affective Disorders

SIR: The article "A *DSM-III* Family Study of the Nonschizophrenic Psychotic Disorders" by Kenneth S. Kendler, M.D., and associates (1) was interesting for its contribution to the ongoing diagnostic issue of schizophrenia versus affective psychosis. I would like to add a viewpoint on the etiology of schizoaffective disorder to those considered on pages 1102–1103 of the article.

Unless schizophrenia and affective psychosis are in some way mutually exclusive, the percentage of schizophrenic patients with affective psychosis as a second, separate illness must be the same as that in the general population, and vice versa. I believe that this group accounts for a small, but almost certainly present, subset of schizoaffective patients. Using the risk values in the paper—0.2% for schizophrenia and 0.3% for bipolar disorder—we can be sure that 0.06% of the population has both diseases. I think the most important thing about this group is that it is consistently ignored, yet isn't the two-disease theory the one that most easily explains the area between the schizophrenic and affective psychoses? The numbers are too small to explain most cases of schizoaffective illness, but I think the viewpoint is valid enough to be included.

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GEORGE S. LAYNE, M.D.
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Dr. Kendler Replies

SIR: Dr. Layne raises a useful point. Certainly, there is no reason why having schizophrenia should convey immunity to affective disorders, or vice versa. Furthermore, he is correct in saying that this should have been included as a possible explanation for at least a subset of cases of schizoaffective disorder. However, as was pointed out previously by Brockington and Meltzer (1), the occurrence of schizoaffective disorder is far more frequent than would be predicted by the simple co-occurrence of schizophrenia and affective disorders. In fact, these authors found that the observed incidence of schizoaffective disorder was apparently more than 100 times that predicted by the co-occurrence theory. This can be illustrated by an error in Dr. Layne's letter. If the risk for schizophrenia is 0.2% and for bipolar disorder 0.3%, then 0.0006% of the population (not 0.06%) would be expected to have both diseases.

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Cortisol and Alzheimer's Disease

SIR: Three major findings appeared in the papers by Davis et al. (1) and Greenwald et al. (2) on cortisol and Alzheimer's disease: 1) there was no relationship between either of their measures of dementia severity and dexamethasone nonsuppression, 2) the nonsuppressing demented patients were significantly older than the suppressors, and 3) the most severely demented patients had the greatest number of major depressive symptoms.

My colleagues and I conducted a similar study (3) and observed different results. We studied the dexamethasone suppression test (DST) in 27 nondepressed patients affected by senile dementia of the Alzheimer type according to Carroll's protocol, with plasma cortisol sampled at 4:00 p.m. The patients were 71–95 years old. They were evaluated for dementia by the Mini-Mental State Examination. Like Greenwald et al. (2), we found that scores on the Hamilton Rating Scale for Depression were uninterpretable, so we used a depressive symptom checklist (4) similar to their depression scale. The items were verbal report, behavior, and secondary signs including major symptoms (loss of interest, lack of reactivity, severe depressed mood) and minor ones (insomnia, poor appetite, ruminative thinking, etc.). Each item was scored from 1 (not at all) to 5 (very much). The depression ratings were done simultaneously by three different physicians, and the final score was the mean value of the three independent evaluations.

We obtained the following results. 1) The most severely impaired patients had significantly higher cortisol values after the DST than the less affected patients. Seven of 16 severely demented patients and none of 11 mildly or moderately affected patients were found to be nonsuppressors. 2) The nonsuppressing demented patients were not older than the suppressors (mean±SD age=82.6±3.7 years and 86.0±7.0 years, respectively). 3) The mean±SD depression scores for the severely demented patients (5.0±2.3) and the mildly or moderately affected patients (4.2±1.8) were not significantly different.

These apparent discrepancies between our study and that of Davis, Greenwald, and associates (1, 2) could be related to methodological or individual nonspecific factors. 1) The heterogeneity of the group of patients studied by Greenwald et al. is important, since the group included presenile and senile patients who were living in the community but who had entered the hospital to receive the DST. In comparison, we studied a very homogeneous group of senile patients who had been living in an institution for at least 3 months. 2) The depression scales used in both studies have a low sensitivity. 3) The authors compared the depressive symptoms with the 8:00 a.m. cortisol level but not with the 4:00 p.m. or 11:00 p.m. level. Two of six patients did not show nonsuppression at 4:00 p.m. or 11:00 p.m. In fact, the postdexamethasone cortisol levels at those two times did not correlate with any depression measure. It has already been shown by Pomara et al. (5) that plasma cortisol measured at 4:00 p.m. is not related to the severity of dementia. The cortisol circadian rhythm could be impaired in senile dementia of the Alzheimer type, and further studies are necessary to clarify this point.

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Dr. Greenwald and Associates Reply

SIR: Dr. Davous's report on the dexamethasone suppression test (DST) in dementia patients adds to a growing and at times conflicting literature on this subject. Eight reports on the DST and dementia were cited in the Greenwald et al. paper (references 10–16 and 18 of that paper). We are now aware of five others, including reports by Georgotas et al. (April 1986 issue of the *Journal*), Moffatt (letters in the August 1984 and April 1985 issues of the *Journal*), Pomara et al. (reference 5 in Dr. Davous's letter), Katona and Aldridge (1), and Alexopoulos et al. (2). Disparate results exist that are probably due in part to inconsistent methodological variables across studies, as Dr. Davous notes in comparing his and our results. These include differences in homogeneity of clinical samples and diagnostic criteria, rating scales and raters, time of blood sampling and number of samples, and dose of dexamethasone. The majority of studies find a high prevalence of DST nonsuppression in nondepressed demented patients and conclude that the test is of dubious value in differentiating either "dementia syndrome of depression" from dementia or dementia complicated by depression from dementia alone.

Dr. Davous's finding of postdexamethasone cortisol suppression in mildly demented subjects and a greater frequency of nonsuppression in more severely demented patients is in agreement with some reports. Although we and others found no relationship between severity of dementia and postdexamethasone cortisol level, Dr. Davous's data suggest that the DST might be clinically useful for a less severely demented group. Of interest are two reports on serial DSTs in demented patients (3, and the Moffatt letters we have mentioned), wherein DST reversal from nonsuppression was associated with antidepressant treatment, but not necessarily response, in selected patients. However, these patients for the most part had advanced disease.

Three findings in our paper were emphasized by Dr. Davous. We would highlight another: the 8:00 a.m. postdexamethasone cortisol level, but not the 4:00 p.m. or 11:00 p.m. level, correlated with major or endogenous depressive symptoms, whereas no relationship was demonstrated with minor symptoms. This result is interesting, since morning cortisol nonsuppression after administration of dexamethasone may be of special diagnostic relevance. For example, nonsuppression of cortisol at 8:00 a.m. after dexamethasone is considered a definitive test for Cushing's syndrome (4). In addition, Stokes et al. (5), in a multicenter study of depressed patients, found that nonsuppression of morning cortisol levels on the DST had as good, or better, diagnostic accuracy as when nonsuppression was defined as one or more of three post-DST levels of 5 μg/dl or more; they suggested exercising greater caution in "the clinical interpretation of nonsuppression based on two (or more) post-DST samples or on samples obtained late in the post-DST day." We would also like to note that our sample, although heterogeneous in that it included presenile-onset and senile-onset cases, was extraordinarily homogeneous in meeting rigorous inclusion and exclusion research criteria for the diagnosis of drug-free and medical-illness-free Alzheimer's disease. Last, as a point of

clarification, Pomara et al. (reference 5 in Dr. Davous's letter), while demonstrating that 8:00 a.m., 1:00 p.m., and 4:00 p.m. predexamethasone cortisol levels were unrelated to severity of dementia, measured only 8:00 a.m. postdexamethasone cortisol and found significantly higher levels in the more demented group.

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Clinician-Researchers in Psychiatry

SIR: We read with great interest the recent article by Jack D. Burke, Jr., M.D., et al. (1) describing the need for training greater numbers of clinician-researchers in psychiatry. The authors successfully identified the important roles that the individual who pursues research training needs to assimilate. Dr. Burke and his colleagues also stated their belief that there may be dangers in initiating research training before the establishment of clinical identity and implied that the preferred time for research training is during a prolonged postresidency period. We agree that good research training requires a longer period than the traditional residency, or even postresidency research fellowship, to accomplish the tasks these authors list. We feel, however, that such training can, and perhaps should, begin at a considerably earlier stage, at least for some individuals. We present an approach for facilitating research training that avoids arresting the development of clinical identity but occurs concurrently with residency training.

The Residency Research Track of the Department of Psychiatry at the University of Michigan is a relatively new program designed to allow selected, qualified residents the opportunity to combine clinical and research training. The research-oriented resident seeks a faculty research mentor and, with guidance from this adviser, writes a research proposal outlining a plan of study that includes both clinical experiences and a research project. The program emphasizes flexibility and seeks to custom-tailor each resident's course of study. The usual plan is for the resident to enter this program in PGY-2. The schedule is then designed to provide 20% research and 80% clinical exposure during PGY-2, 30% research and 70% clinical during PGY-3, and 50% of each during PGY-4. To complete the clinical education, a 5th postgraduate year is added, with 70% research and 30% clinical time allocations. These ratios are, of course, only rough guidelines. The ambitious resident who enters such a program must, not surprisingly, spend a number of free nights and weekends to successfully master the "dual" workload. We feel that the sanctioned reduction in clinical duties is essential; without this, the investigator-in-training often feels overwhelmed, and either clinical training or the research project suffers. By providing the reduction in clinical load, protected time can be created for staged learning of research principles. Simultaneously, the addition of the 5th year provides continued clinical experience to compensate for the reduction of clinical load in earlier years.

The design of this track is based on the beliefs that few important research questions can be answered with brief, cross-sectional studies; that clinical research training requires a longitudinal perspective, and the longer the training period, the better; that research studies are ideally integrated with clinical delivery; and that fragmentation of the trainee's work into "clinical" and "research" worlds interferes with integrated thinking. Although this type of program will not completely train individuals to be clinician-investigators, it starts the process for suitable candidates. It allows the trainee to begin to assimilate the tasks outlined by Dr. Burke and associates as necessary for the development of the professional identity of the clinician-researcher, but at an earlier stage in training, thus promoting the simultaneous development of the individual as both a clinician and an investigator.

There is a tremendous need for adequately trained clinician-researchers in psychiatry, especially as advances are made in psychobiology and the neurosciences. We agree with Dr. Burke and his colleagues that the prospective clinical investigator needs to overcome a number of developmental hurdles. We feel that our research track model may be one possible approach to these hurdles, facilitating the development and fusion of clinician and researcher identities.

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JAMES H. MEADOR-WOODRUFF, M.D.
JOHN F. GREDEN, M.D.
Ann Arbor, Mich.

SIR: I agree with most of the conclusions and recommendations of Dr. Burke and his associates in their article on the clinician-researcher. However, I think they do a disservice by concentrating solely on the academic clinical researcher and ignoring the important role that the psychiatrist–basic scientist should (and I hope will) play in the future of psychiatry. Clinical research in psychiatry is clearly of critical importance, yet despite a fairly sustained research effort over the last 20 years, we have learned relatively little about the etiology and pathophysiology of psychiatric disorders. Neurochemical and neuroendocrine studies have found abnormalities that are generally too heterogeneous to be of diagnostic or etiologic significance. Despite extensive research, essentially no new psychotropic agents have been discovered that are more efficacious in treating schizophrenia or depression and have fewer unwanted side effects than drugs that have been in clinical use for more than 20 years. Even the recent suggestion that schizophrenia may be subdivided according to the predominance of positive or negative symptoms and the ventricle-brain ratio is being called into question (1).

I believe it is not unreasonable to suggest that the relative lack of progress in clinical research is secondary to our

inadequate and relatively unsophisticated understanding of basic brain processes at both the cellular and the systems levels. A corollary of this is that a more sophisticated understanding of the brain and its cellular processes should generate more heuristically useful hypotheses. Academic psychiatry departments should be encouraged to develop and support the basic neurosciences. Specifically, there is a need for psychiatrists with rigorous training in a variety of basic neuroscience disciplines. In general, neurobiologists without clinical training have little understanding of the underlying complexity subsumed in diagnoses such as schizophrenia or borderline personality disorder. They also do not understand the issues facing clinicians when they must decide what medication to give, in what dose, and for what duration of time. Obtaining both clinical and basic science training should enable researchers to frame questions that are of clinical importance yet can be answered rigorously at more basic levels. A psychiatry department with neurobiologists and clinical researchers working together is likely to make far greater progress than one that neglects either discipline.

By emphasizing the need for research in basic neuroscience I do not mean to negate the importance of psychosocial influences on the development and outcome of psychiatric disorders. However, in this era of fiscal restrictiveness and vigilance, it is important to assign priorities to the appropriation of mental health research funds. I predict that the highest cost-benefit ratio will eventually be found to accrue from investments in basic neuroscience.

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ROBERT C. MALENKA, M.D., PH.D.
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Dr. Burke and Associates Reply

SIR: We are pleased to have Dr. Meador-Woodruff and Dr. Greden describe their combined clinical and research training program, and we hope it is successful. In our view, adding a 5th year to such a residency in order to provide a longitudinal experience for trainees in both their clinical and their research tasks is appropriate. We feel, however, that everyone calling himself or herself a psychiatrist should have substantial clinical training and that these needed research experiences should not come at the expense of experiences necessary for establishing a clinical identity. With that goal in mind, we think the timing and sequence of clinical and research experience can certainly be flexible.

With regard to Dr. Malenka's letter, in our view, most clinician-researchers in psychiatry will be highly trained in at least one basic science, including neuroscience, psychology, epidemiology, etc. In recognition of the increasingly rapid progress made in psychiatric research over the past decade, we cannot endorse Dr. Malenka's somewhat harsh critique of contemporary researchers. Rather than criticizing the past, we hope for sustained momentum in the future. We do agree on the importance of continuing and expanded efforts to strengthen the link between neuroscience and clinical psychiatry; that issue has been directly addressed by one of us in a subsequent issue of this *Journal* (1). We are confident that the training of new researchers who have a clinician's grasp of psychiatric disorders will generate further advances in the next decade as well.

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Reliability of Axis V of *DSM-III*

SIR: In their recent article in this journal, Thakshan Fernando, M.B., et al. (1) reported an intraclass correlation coefficient of reliability of .49 for axis V of *DSM-III*, puzzlingly different from the .69–.80 values obtained in the *DSM-III* field trials (2). An intraclass correlation coefficient represents the ratio of true variance in the population studied to that variance plus error variance. Therefore, reliability is in part a function of the variability of the sample studied. For this reason, in order to understand their findings, it would be helpful to know the authors' estimates of the magnitude of these components of variance. This would enable anyone to compare their findings with those of Dr. Fernando and associates and begin to understand the source of any differences.

In the *DSM-III* field trials, although estimates of the components of variance were not reported, a wide range of patients in terms of both diagnosis and clinical setting (inpatient, outpatient, specialty clinic, etc.) were included, and thus there was great variability in the subjects evaluated. Fernando et al. reported that their sample consisted entirely of "consecutive admissions to the psychiatric unit of a general hospital," a relatively homogeneous group in many respects. This lack of variability could at least partially account for their finding of low reliability.

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JANET B.W. WILLIAMS, D.S.W.
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Clonazepam: An Antidepressant?

SIR: In a recent letter to the Editor, Mark Zetin, M.D., and Matthew J. Freedman, M.D., (1) raised the hypothesis that clonazepam "may have antidepressant ... effects" while reiterating the now widely accepted antimanic properties of that benzodiazepine. In the two cases presented by Drs. Zetin and Freedman, it clearly appears that the depressive symptoms and signs reported by both patients could be explained

more accurately as the "decline phase" of a cyclical bipolar disorder. From those two cases it cannot be inferred that clonazepam is efficacious as an antidepressant.

Jones and Chouinard (2) have more appropriately addressed the matter of the antidepressant properties of clonazepam, although anxiety predominated in their case report. We (3) have reported the successful addition of clonazepam to the treatment regimen of a patient afflicted with major depression who had not responded to antidepressants and/or neuroleptics. This report, too, indicated that the patient's illness was not a clear and unblemished depression; the patient had borderline personality traits and polysubstance abuse.

Clonazepam is most effective in treating the following spectrum of symptoms: hyperactivity, agitation, intrusiveness, impulsivity, episodic violence, hypersexuality, grandiosity, logorrhea, and anxiety. This "manic spectrum" overlaps various diagnostic categories, including bipolar disorder, manic, schizoaffective disorder, anxiety disorders, borderline personality disorders, etc. Clonazepam is thus symptom-specific rather than syndrome-specific (3, 4).

The biochemical correlates of this manic spectrum reside within the serotonergic neurochemical system (3–5). Clonazepam is serotonin enhancing, thus mimicking lithium, and its potent benzodiazepine receptor binding could account for its direct anxiolytic action. In addition, it has anticonvulsant (antikindling?) and sedative properties. A summation and/or synergism among all these properties most likely produces the desired therapeutic results. Furthermore, clonazepam is probably the safest benzodiazepine available.

In summary, clonazepam is a safe and effective anti-manic-spectrum agent. Its antidepressant effect is as yet unknown. The evidence so far suggests that, in all likelihood, no such antidepressant activity exists.

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The AIDS Virus and the CNS

SIR: I read "Three Cases of AIDS-Related Psychiatric Disorders" by James R. Rundell, M.D., and associates (1) with interest. Since their article was submitted there have been several reports that human T-lymphotropic virus-type III (HTLV-III) may infect the CNS, causing a myelopathy (2), a neuropathy (3), and an encephalopathy that progresses to dementia (4, 5).

Acquired immune deficiency syndrome (AIDS) encephalopathy is now regarded as the most common neuropsychiatric complication; it occurs in about one-third of patients with AIDS (6). The condition is characterized by subtle cognitive changes, confusion, headache, malaise, lethargy, loss of libido, social withdrawal, depressed mood, and personality change progressing over weeks or months to dementia with fits and ataxia.

Do Dr. Rundell and his colleagues feel that a neurotropic effect of the virus could have been responsible for the organic brain syndrome in case 1 and the depression in case 2?

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CHRISTOPHER S. THOMAS, M.B.B.CH., M.R.C.PSYCH.
Manchester, England

Dr. Rundell and Associates Reply

SIR: Dr. Thomas's observations on our report give us an opportunity to expand our comments concerning neuropsychiatric manifestations of AIDS and AIDS-related disorders. Since our report was written, it has been confirmed that HTLV-III can directly infect cells in the central nervous system (1, 2). This evidence has stimulated further inquiry into the effects of the virus on the brain as revealed by mental status examination. We can add knowledge of direct CNS effects to our awareness of indirect effects such as AIDS-related opportunistic infections and tumors and psychological reactions to HTLV-III infection. In a recent development, both the presence and the production of the virus were demonstrated in cultures from a brain biopsy of a patient with diffuse encephalopathy followed by progressive dementia (3).

It is our impression that our first patient's mixed organic brain syndrome (concentration/attention difficulty, lack of abstract reasoning, suspiciousness, spelling difficulty, expressive dysphasia, impaired concept formation, and diminished right upper extremity motor speed) was due to HTLV-III encephalopathy. No evidence exists that a CNS neoplasm or opportunistic infection was present.

Our second patient met *DSM-III* criteria for an episode of major depression that began shortly after a diagnosis of AIDS had been made. He had no prior history of affective illness. We believe that his intense anger and suspiciousness was a reflection of prominent preexisting maladaptive personality traits, not HTLV-III infection. Decreases in his levels of anger and suspiciousness and in the severity of his depression followed psychotherapy. (He declined antidepres-

sant medication.) Although dysphoria, paranoia, and personality change have been reported as chronic sequelae of other viral encephalopathies (4), we do not believe that our second patient had an encephalopathic process, nor do we believe that his depression was a direct effect of the virus on the CNS. However, given the neurotropic nature of HTLV-III and the increasing number of cases of AIDS and HTLV-III infection, it is certain that affective, cognitive, and other neuropsychiatric symptoms will be commonly encountered.

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β-Adrenergic Blockers for Aggressive Behavior in Schizophrenia

SIR: The article "β-Adrenergic Blockers for the Control of Aggressive Behaviors in Patients With Chronic Schizophrenia" by Paul J. Sorgi, M.D., and associates (1) prompted us to review our experience with similar patients and to speculate on the mechanism of action of these agents.

At this forensic inpatient facility, we have treated three chronically aggressive psychotic patients with propranolol in conjunction with neuroleptic medications. Two patients, both of whom were also mentally retarded, failed to respond despite prolonged treatment with doses of more than 600 mg/day.

The third patient, a 30-year-old man with a diagnosis of paranoid schizophrenia, had a long history of psychosis with command hallucinations and unpredictable assaults, despite treatment with large doses of neuroleptic medications. In 1 month he had 43 separate aggressive episodes and required seclusion on 26 occasions. When propranolol was gradually added, his symptoms rapidly remitted, including a complete disappearance of assaultive behavior. This improvement has been maintained for more than 2 years and has permitted the patient to go out into the community for the first time since being hospitalized. His symptoms recurred when we attempted to reduce the dose below 400 mg/day. He has experienced no significant bradycardia or hypotension. Fluphenazine decanoate, 25 mg every 2 weeks, has been concurrently prescribed.

Our experience thus tends to confirm the findings of Dr. Sorgi and associates, and of others, that β blockers can be of considerable benefit in treating some schizophrenic patients—particularly those with aggressive symptoms—who have been refractory to treatment with neuroleptics alone.

Regarding the mechanism of action of β blockers, it appears to us that four possibilities may be entertained: peripheral autonomic blockade, central antiadrenergic or other activity, an effect on akathisia, and/or pharmacokinetic interaction with neuroleptics.

Dr. Sorgi and his colleagues suggested that the effect may be peripheral, noting that their patients were treated with nadolol, which, in contrast to propranolol, is quite lipophobic. Despite this, nadolol does appear in important concentrations in the CSF (unpublished observations, Squibb Institute for Medical Research), as does atenolol, a similar but even more lipophobic drug (2). Thus, for all these agents, a central locus of activity cannot be ruled out (3). Dr. Sorgi's group has noted that nadolol is effective in treating akathisia (4). This action could diminish aggressive behavior by decreasing extrapyramidal motor activity. Finally, β blockers may act by increasing the plasma level of neuroleptics. Propranolol is known to cause a doubling of phenothiazine levels, apparently by competing with neuroleptics for liver enzymes (5). However, nadolol, in contrast to propranolol, is not metabolized by the liver (6) and thus may not have this effect. To resolve this issue, it will be necessary to obtain neuroleptic serum levels.

We are not aware of any controlled studies in which schizophrenia (with or without aggressive behavior) has been successfully treated with adrenergic blockers alone. We note that Dr. Sorgi and colleagues' patients also received neuroleptics. The question of whether β blockers have inherent antipsychotic or antiaggressive activity remains unresolved at this time.

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SIR: I read with some interest the paper by Dr. Sorgi and his colleagues in which they described their success in using β-adrenergic blockers for the treatment of aggressive behavior in patients suffering from chronic schizophrenia. My colleagues and I obtained similar findings in a double-blind, placebo-controlled trial that was carried out to examine the value of propranolol as an adjunct to neuroleptic medication in the treatment of patients suffering from chronic schizophrenia who still had active symptoms. We reported our findings in 1983 (1).

Patients were treated with up to 320 mg of propranolol twice a day for 12 weeks. Propranolol was found to have a more beneficial effect than placebo, but the results were not as dramatic as those shown in previous studies (2). Interestingly, we found significant differences in favor of propranolol on the irritability scale of the Nurses' Observation Scale for Inpatient Evaluation (3) at weeks 4 and 5, which is in keeping with the findings of Dr. Sorgi and associates. The findings of Peet et al. (4) may explain these results. They demonstrated a pharmacokinetic interaction whereby plasma levels of chlorpromazine, total pharmacologically active neuroleptic compound in serum, and serum prolactin were markedly and significantly raised during treatment with propranolol. Nevertheless, there is some evidence that β-adrenergic blockers do have an intrinsic antipsychotic effect. In view of the large numbers of patients suffering from schizophrenia who do not improve with neuroleptics, this work must be of great value, and studies should continue.

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Dr. Sorgi and Associates Reply

SIR: Drs. Whitman, Maier, and Eichelman have provided an illuminating case report. As they noted, it is persistently aggressive patients who benefit most from the β-adrenergic blockers. This aggression is driven and almost compulsive. The patients who benefit are psychomotorically irritable, easily aroused, tense, and overactive. Patients who exhibit planned or purposeful aggressive behavior do not respond. We wonder whether the two patients mentioned by Dr. Whitman and associates who did not respond lacked the profile that we associate with response. As Dr. Pugh notes in his letter, these findings were supported and predated by his 1983 study. In fact, reviewing the literature on β blockers used to treat schizophrenia, we reported (1) that it is only those studies which measure agitated, assaultive, or irritable behavior as an outcome variable that find a therapeutic effect of the β-adrenergic blockers in schizophrenia.

The points made by Dr. Pugh and by Dr. Whitman and colleagues with regard to the concomitant use of neuroleptics are important and well taken. We have noted a general reduction of neuroleptic dosage in patients treated with β blockers (1). The use of parenteral antipsychotics did not affect behavior, however, which suggests that reduction in first-pass metabolism in the liver does not explain this effect. We have noted that stopping either the neuroleptic or the β blocker has resulted in reemergence of aggressive behavior (2). Our feeling is that in a psychotic patient, both agents are required to ameliorate aggressive behavior. To us this suggests a synergistic effect more complicated than a simple elevation of blood level.

As Dr. Whitman and associates indicate, nadolol penetrates into the CNS, so lipid solubility cannot be used to infer site of action. It is clear, however, that nadolol does have profound effects on peripheral autonomic variables (3). We suggest that impulsive aggression may result when excessive internal stimulation from hyperactive autonomic receptors is conducted afferently into the CNS, thereby overwhelming fragile cognitive processes. This results in a degeneration of the ability to integrate sensation, cognition, and motor response. Under these circumstances, any environmental stress may lead to a poorly integrated impulsive motor response, i.e., aggressive behavior. We suggest that nadolol and the β blockers work by dampening peripheral autonomic input into the CNS, thereby facilitating cognitive integration and control of motor response. In this model, nadolol works peripherally to influence central processes.

This type of interplay between peripheral autonomic activity and cognitive behavioral controls has been postulated in the psychophysiology literature (4, 5). It has been shown that afferent input to the CNS from visceral autonomic receptors can impede cognitive–sensory-motor integration, which subsequently produces increased motoric impulsivity. Admittedly, this is a basic science model, far from a clinical situation, but to us the parallels are intriguing.

Whether the β blockers influence this process centrally or peripherally is unclear. What does seem to happen, though—concomitant with amelioration of aggression—is a general quieting of autonomic and somatic reactivity.

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Hemoglobin and Erythrocyte Indices in Panic Disorder

SIR: Daniel B. Carr, M.D., and associates (1) reported that hemoglobin differed significantly between panic disorder patients and control subjects. They suggested that mild erythrocytosis may be a previously overlooked dimension of untreated panic disorder and may be linked to the reported increase in mortality and morbidity of anxiety disorder patients due to circulatory system disease (2, 3). Increased hemoglobin values have been previously associated with anxiety, tension, and psychological stress (4).

We compared the hemoglobin level, mean cell volume, mean cell hemoglobin, mean cell hemoglobin concentration, and score on the State-Trait Anxiety Inventory (5) of 49 patients with panic disorder to those of 27 healthy control subjects. There were 22 male and 27 female patients and 16 male and 11 female control subjects. The mean±SD age of the patients was 32.4±7.5 years; for the control subjects it was 29.4±6.8 years. We compared these values when the subjects were at rest and just before lactate, isoproterenol, and dextrose infusions. We always compared male patients with male control subjects and female patients with female control subjects. Data were analyzed by two-way analysis of variance (ANOVA).

There was a statistically significant difference between the mean±SD anxiety scores of the male patients and those of their control subjects (rest: 50.9±11.1 and 23.4±3.5; $F=100.77$, df=1, 36, $p<.01$) and between the mean±SD anxiety scores of the female patients and those of their control subjects (rest: 52.8±12.4 and 23.9±3.6; $F=70.48$, df=1, 36, $p<.01$).

However, there were no significant differences between the male patients and control subjects in the following mean± SD values: hemoglobin level (rest: 15.7±1.0 g/dl and 15.5±1.1 g/dl; $F= 0.88$, df=1, 36), mean cell volume (rest: 90.7±5.0 μm^3 and 91.2±3.7 μm^3; $F=1.59$, df=1, 36), mean cell hemoglobin concentration (rest: 34.2±1.0% and 34.0±0.8%; $F=1.60$, df=1, 36), and mean cell hemoglobin (rest: 30.7±1.5 pg and 30.8±0.9 pg; $F=0.16$, df=1, 36).

There were also no significant differences between the female patients and control subjects in the following mean±SD values: hemoglobin level (rest: 13.5±1.2 g/dl and 13.3±1.3 g/dl; $F=0.08$, df=1, 36), mean cell volume (rest: 89.8±4.6 μm^3 and 90.1±6.0 μm^3; $F=2.03$, df=1, 36), mean cell hemoglobin concentration (rest: 34.2±1.7% and 34.3±1.2%; $F=2.74$, df=1, 36), and mean cell hemoglobin (rest: 30.8±1.5 pg and 30.5±1.9 pg; $F=0.13$, df=1, 36).

The results of an overall ANOVA of hemoglobin and erythrocyte indices for all patients and all control subjects were not significant. There was no correlation between anxiety scores and hemoglobin indices in panic disorder patients (Pearson's $r=.005$ for resting values).

These results do not support earlier reports that hemoglobin levels are higher in patients with panic disorder. Increased mortality and morbidity in panic disorder patients might have a different underlying physiological mechanism from increased hemoglobin and hemoconcentration.

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More on Standard Deviation Versus Standard Error

SIR: Beginning in January 1986, the *Journal* has required authors to report the statistical standard deviation rather than the standard error of the mean (1). There is ample rationale for such a policy in studies that use a relatively small number of subjects, which is often the case in studies published in the medical literature. There is, however, an important exception to this rule of thumb: the reporting of data from large surveys that use complex sampling. Such surveys include those done by the U.S. Bureau of the Census, the National Center for Health Statistics, and the National Institute of Mental Health (NIMH). An example is the NIMH Epidemiology Catchment Area Survey (2).

As noted in the *Journal* editorial supporting the use of the standard deviation (1), when an investigator reports on a small sample, the standard deviation will "assist the reader in appreciating an immediate sense of the data." In addition, the statistical standard deviation remains the same regardless of sample size, because it is a relatively unbiased estimate of the standard deviation of the underlying population being studied, not of the sample.

However, in reports of data from a large survey that are the result of a complex sampling methodology, it is no longer clear what a standard deviation represents, because there are separate components of variance from each of the levels of the sampling design. This has been termed "design effect" (3). A summary measure of dispersion is therefore needed that takes into account not only deviations from the mean but also the sampling errors from each part of the survey. The latter is necessary because the object of any study is to estimate the mean of all portions of the design taken together. In statistics this measure is called the standard error of the mean.

An important characteristic of the standard error derived in this way is that it is itself a random variable, which is normally distributed and has a constant variance (4). As the sample size increases, the tendency to be normally distributed increases (the central limit theorem), meaning that the standard error can be used in hypothesis testing with standard statistical tests.

It should be pointed out that a standard error derived as I have indicated shares some of the properties of a standard error derived for a small, simple random sample. (For example, it does decrease as sample size increases.) It is, however, calculated in a much more complex way than dividing the standard deviation by the square root of the sample size, as is done in small-sample statistics.

Finally, in some standard statistics books, which are oriented toward small-sample statistics and tend to use theoretical statistical terminology, the standard error is regarded as almost identical to the standard deviation: the standard deviation refers to a population and the standard error refers to a simple random sample (5). The use of these terms as almost synonymous, however, is not the sense in which I and Dr. Bartko (1) use the term.

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Dr. Bartko Replies

SIR: The standard deviation is a measure of the variation of a set of *data*, whereas the standard error is a measure of the variation of parameter estimates. Thus, the variation of the arithmetic mean, which is an estimate of the population (parameter) mean, is often expressed in standard error terms. Similar standard error language is used with estimates of other parameters such as correlation coefficients, proportions, the slope of a regression line, regression coefficients, and sample survey values.

The use of one term or the other—standard deviation or standard error—is not a function of sample size (i.e., whether the study is small or large) but depends on whether one is describing dispersion in the data or the dispersion of statistical estimates.

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Rape and Multiple Personality Disorder

SIR: In a recent paper (1), Deborah S. Rose, M.D., illuminated the complicated psychodynamics and psychopathology of rape victims, which occur at every developmental level. I have been able to confirm her findings in the psychotherapy of several adult patients with multiple personality disorder who were raped and abused as children. Further, I have found the same picture in an adolescent patient as the result of a pediatric rectal examination made when the patient was 8 years old. This also confirms Dr. Rose's contention that the pathology can persist essentially unimproved for several years.

However, Dr. Rose seemed to focus primarily on rape as a recent event in the life of an adult. The patients I have just referred to were raped as children. Child abuse, both by family members and by others outside the family, appears to be much more prevalent than most of us have wished to admit. It may be that the largest segment of the population which suffers rape is composed of children and adolescents. Of these, a great number will never find their way to a crisis center, because incestuous families typically keep the abuse secret, and multiple personalities typically conceal themselves.

Child abuse—physical, sexual, or psychological—may be the precipitating event in the genesis of a multiple personality disorder, but we often find clinically that the original traumas have been repressed. Further, fugue states and intrusive thoughts, feelings, and actions are frequently found in multiple personality disorder. Fear of loss of control over cognitive processes, affects, and actions should also bring multiple personality disorder into the differential diagnosis, since these phenomena represent the conscious perception of a host personality as alternative personalities struggle for control (2). Some of the patients Dr. Rose described demonstrated these symptoms and may have had multiple personalities before the rape that was reported on.

Rape victims who demonstrate such phenomena should be watched carefully for further signs of multiple personality disorder, because if that diagnosis is correct, effective psychotherapy must be even more far-reaching than Dr. Rose implied.

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Psychiatric Problems of Medical Students and Their Spouses

SIR: I was delighted to see the two recent articles on psychiatric distress in medical students by Lon R. Hays, M.D., and associates (1) and Kathryn Kris, M.D. (2). Like Dr. Robert Arnstein, who wrote the accompanying editorial, I think that this subject has received less attention than it should.

Dr. Hays and colleagues noted that the 11 spouses and significant others in their study were all women and asked whether wives of male students have a more difficult adjustment than husbands of female students or whether men may be more reluctant to seek therapy. I would suggest that husbands have no more or no less difficulty adjusting to their wives' progressing through medical school than wives of male students but that they handle it differently. In my work with husbands of female physicians (3), I have found that some men who married when their wives were in medical school had concerns for years but never said anything. I therefore endorse Hays and associates' recommendation that we make supportive outreach programs available to husbands of medical students.

In her paper, Dr. Kris noted that some students sought help in response to negative behavior on the part of psychiatric instructors. I have found the same, but hasten to add that "medical student abuse" (4) comes from all branches of medicine. When medical students start learning psychiatry, they not only identify with the problems of the patients and their families but they begin to meet physicians who are skilled in biopsychosocial medicine. Further, if they are fortunate, they will have well-balanced instructors who are not intimidating, who treat them with respect, and who are comfortable showing feelings in their work with patients. I think this combination of forces contributes to medical students' readiness to seek professional help themselves.

Today's medical students are tremendously stressed. Many are unsure of themselves and feel overwhelmed by the increasing technology and impersonal nature of the teaching setting and workplace. Some are adult "children of divorce" and are struggling with relationships in their own lives. Some are in serious academic difficulty as they grapple with the information explosion in undergraduate medical education. Many are in debt—to the tune of $30,000 by the time of graduation (5)! Finally, some of their teachers are not in

touch with the everyday realities of the students' lives: "Medical students aren't like they used to be; they don't seem as dedicated or tough; they bellyache a lot."

Let me close with excerpts from a letter to the editor of our local newspaper, written by the mother of a medical student at our university who committed suicide (6).

> I am one of those who had an empty chair at the Christmas table because their son or daughter, brother or sister died as a victim of suicide.
>
> She was 25. The entire medical faculty was shaken to the core. At a memorial service, many came to me and said, "But why?" and "Had I known. . . ."
>
> We rush around day by day, our lifestyles hurried and exhilarating—even her classmates didn't notice her missing for two days. We have no time to listen to the needs of others, to the lonely ones.
>
> May her tragic death always remind us that the despair hiding in a heart can become too great to show and too complicated to ask for help.

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Corrections

In the article "Mutism: Review, Differential Diagnosis, and Report of 22 Cases" (November 1986 issue, pp. 1409–1414), by Lori L. Altshuler et al., there was a printing error. The second sentence of the first complete paragraph in the right column of p. 1409 should read ". . . neuroleptic agents (16–19) . . ." rather than "neurologic agents."

In the article "Frequency and Presentation of Depressive Symptoms in Patients With Primary Degenerative Dementia" (January 1987 issue, pp. 41–45), by Lawrence W. Lazarus et al., several words were omitted from a sentence in the final paragraph (p. 45). The sentence should read: "Greater importance might be placed on intrapsychic signs and symptoms and less emphasis placed on endogenous or vegetative symptoms, since the former may be more reliable discriminators of depression in these patients."

In the article "Levels of Emotional Awareness: A Cognitive-Developmental Theory and Its Application to Psychopathology" (February 1987 issue, pp. 133–143), by Richard D. Lane and Gary E. Schwartz, there were several errors. On p. 135, in the third line of the bottom paragraph of the left column, the word "possess" should have been "process." Toward the top of p. 136, left column, the line should read ". . . has been described by Werner and others (26–28). . . ." On p. 138, in the middle of the first paragraph in the right column, the phrase should read ". . . clearly differentiated from one another . . ." rather than "closely differentiated." In the middle of the bottom paragraph on p. 141, the term "double depression" should replace "double expression," and in the final line of that paragraph, "course of the affective disorder" rather than "cause of the affective disorder" is correct.

In the article "Sleep Reduction as a Final Common Pathway in the Genesis of Mania," by Thomas A. Wehr et al. (February 1987 issue, pp. 201–204), an incorrect date was cited for the lead quote by Wilhelm Griesinger. The correct date should be 1855.

The staff regrets these errors.

Reprints of Letters to the Editor are not available.

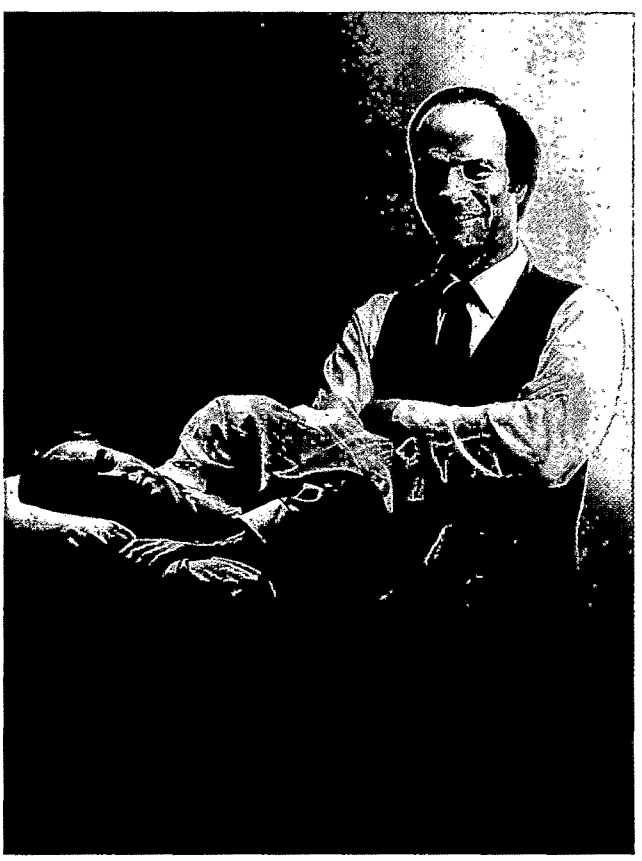


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Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE: *Controlled Substance:* HALCION Tablets are a Controlled Substance in Schedule IV. *Abuse and Dependence:* Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE: Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measure when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

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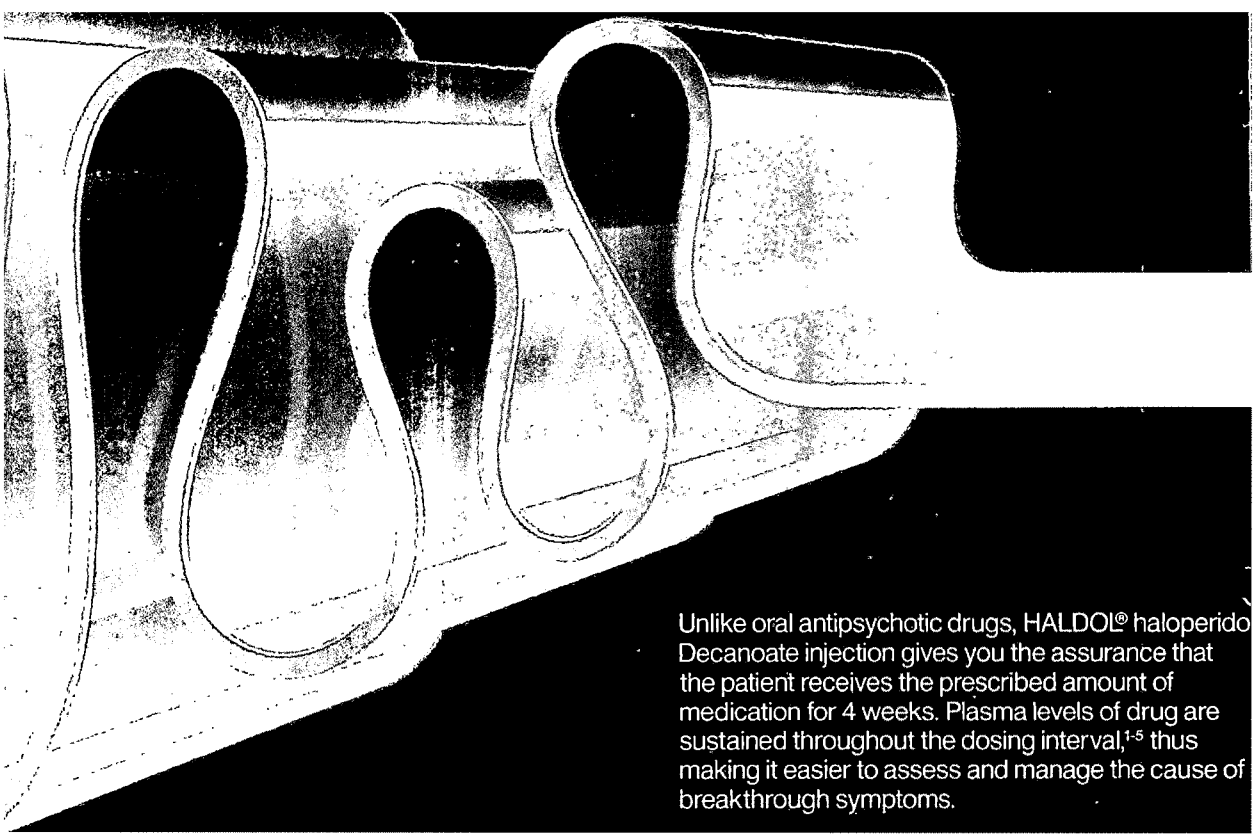
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Barry Reisberg, MD New York University School of Medicine	**Behavioral Symptomatology of Alzheimer's Disease**
Murray A. Raskind, MD (Chairperson) University of Washington	**Dementia Patients and Antipsychotic Drugs**
Carl Salzman, MD Harvard Medical School	**Treatment of Agitation in the Demented, Psychotic Elderly Patient**
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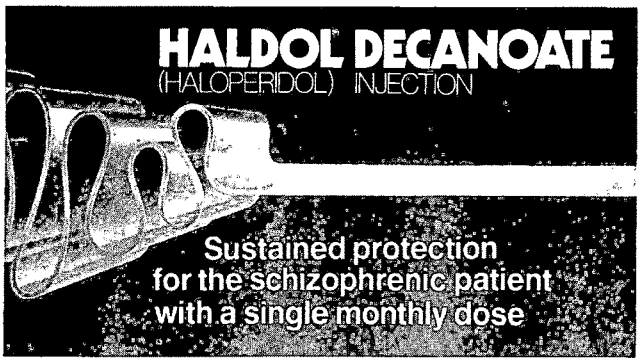
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Please see brief summary of prescribing information on next page.

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The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5 and 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis: the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia and tardive dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Other CNS Effects:* Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic Malignant Syndrome: As with other antipsychotic drugs, a symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported. Cardinal features of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. NMS is potentially fatal, requires intensive symptomatic treatment and immediate discontinuation of antipsychotic treatment. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported. *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

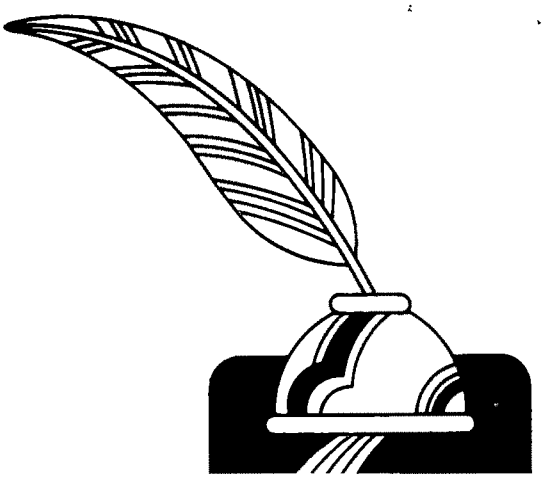
IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

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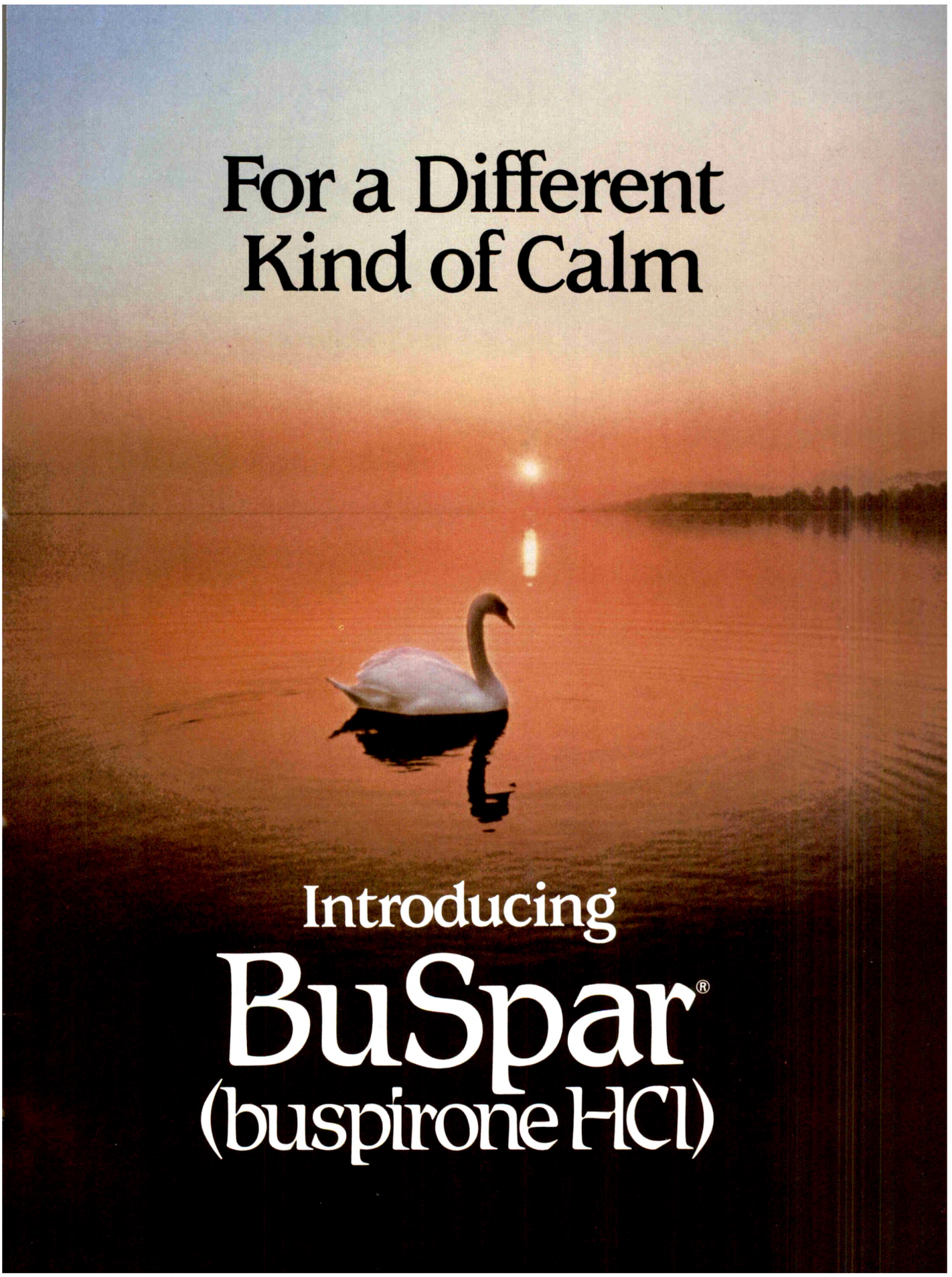
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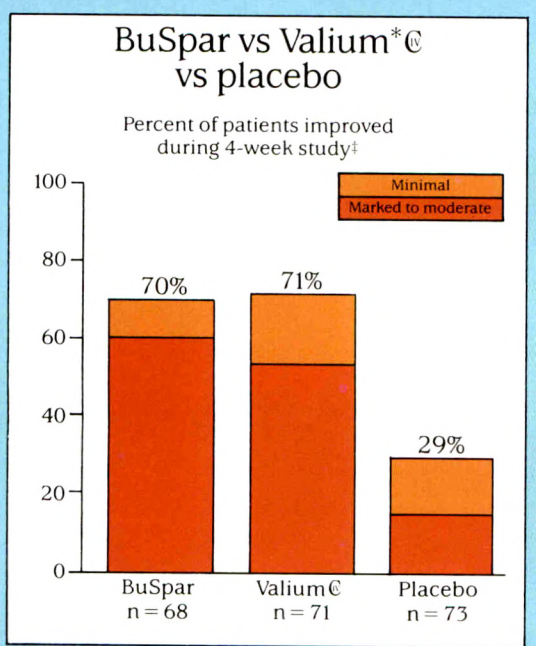
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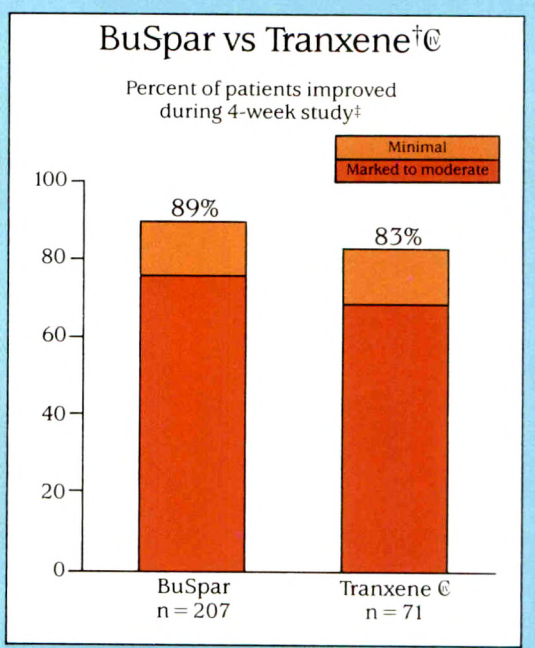
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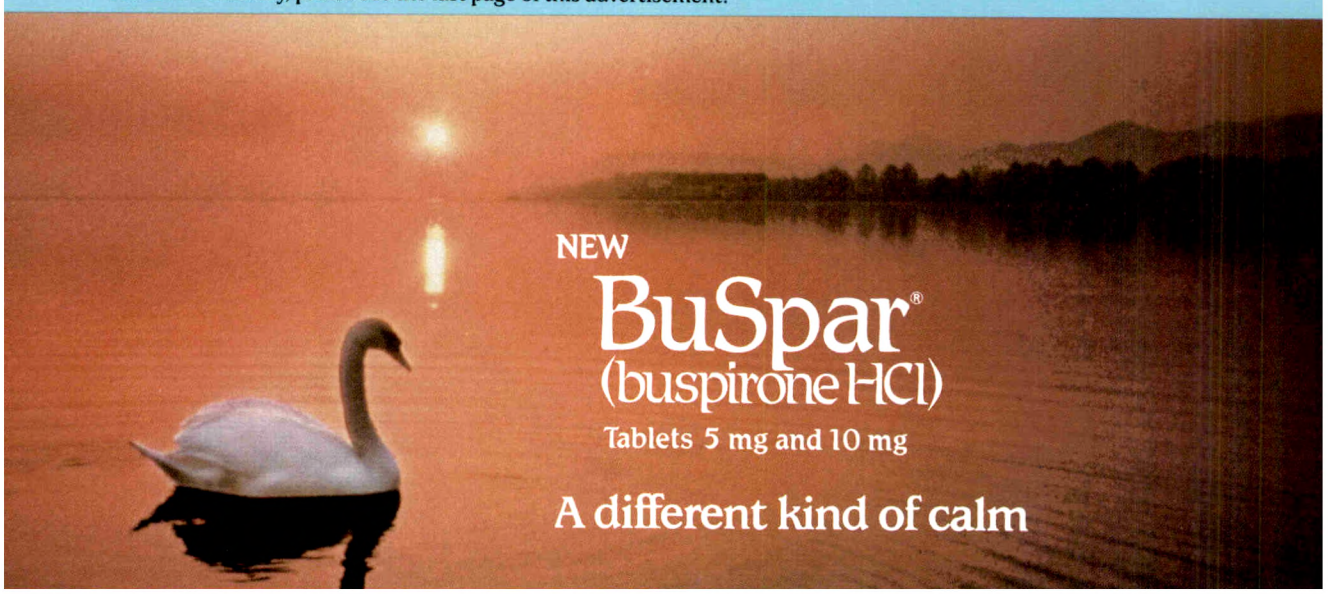




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NEW

BuSpar®

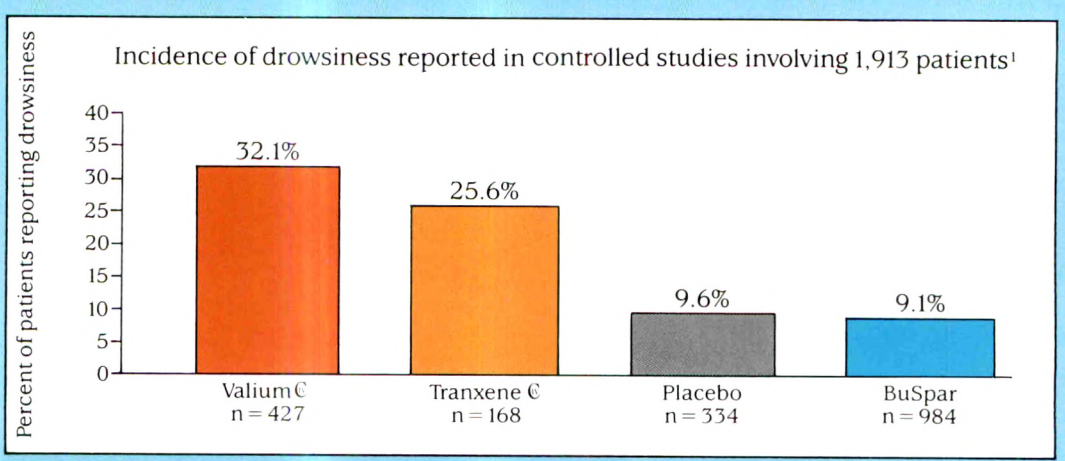
Tablets
5 mg and 10 mg

(buspirone HCl)

Anxiolytic efficacy without CNS-depressant activity

Incidence of drowsiness no greater than placebo

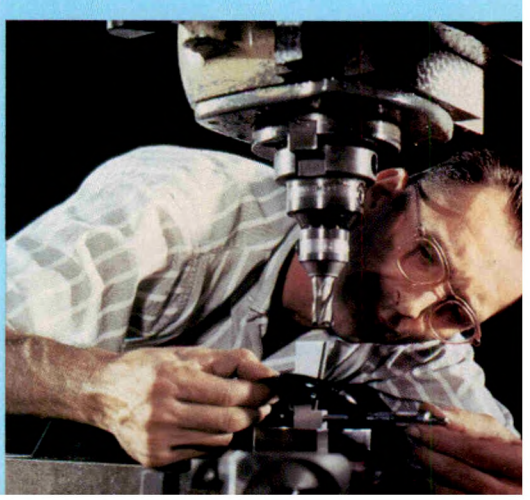
Because BuSpar does not replace symptoms with sedation, patients are alert and aware as well as anxiety-free during their waking hours.[1]



No impairment of motor skills

Controlled studies show that, unlike diazepam, BuSpar did not interfere with driving skills in normal subjects.[2]

NOTE: Patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.





No potentiation of the effects of alcohol

Controlled studies in normal subjects showed that, unlike lorazepam, BuSpar did not augment the effects of alcohol.*[3]

No apparent abuse liability

Extensive preclinical information and clinical data from studies in two populations, recreational users of sedatives and alcohol-dependent patients, demonstrate that BuSpar does not have the characteristics of common substances of abuse. Therefore, BuSpar is not a controlled substance.[4,8]

Well tolerated...with a low incidence of troublesome side effects

The most commonly observed adverse effects in controlled trials were dizziness (12%), nausea (8%), headache (6%), nervousness (5%), light-headedness (3%), and excitement (2%).

*While formal studies of the interaction of BuSpar with alcohol indicate that BuSpar does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and BuSpar.

For Brief Summary, please see the last page of this advertisement.



NEW

BuSpar®

Tablets
5 mg and 10 mg

(buspirone HCl)

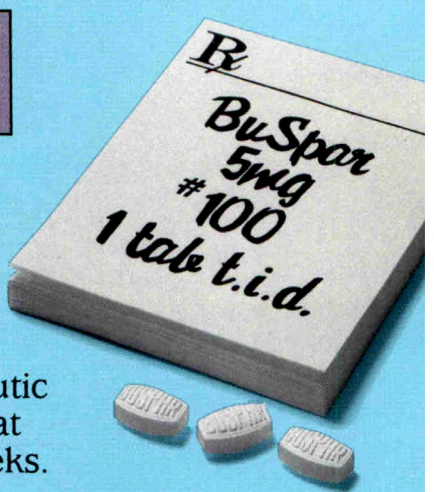
Subtle onset of effect

BuSpar relieves the symptoms of anxiety gradually and steadily. Generally, improvement will be noticeable within 7-10 days.

Prescribing recommendations

Initial dosage—5 mg t.i.d.

Week 1	5 mg	5 mg	5 mg



Dosage adjustment—5 mg/day increments, every 2-3 days, as needed, up to 60 mg/day.

Optimal daily dose—20-30 mg in divided doses, in most patients.

Length of therapy—To achieve full therapeutic benefit from BuSpar, it is recommended that treatment be prescribed for at least 3-4 weeks.

At the end of therapy

BuSpar therapy may be discontinued by simply stopping administration.

BuSpar is <u>not</u> a controlled substance.

Patient selection

BuSpar will not block benzodiazepine withdrawal syndrome... therefore, the best candidates for BuSpar are those not currently taking benzodiazepines.

If you elect to switch a patient from a CNS-depressant drug to BuSpar:

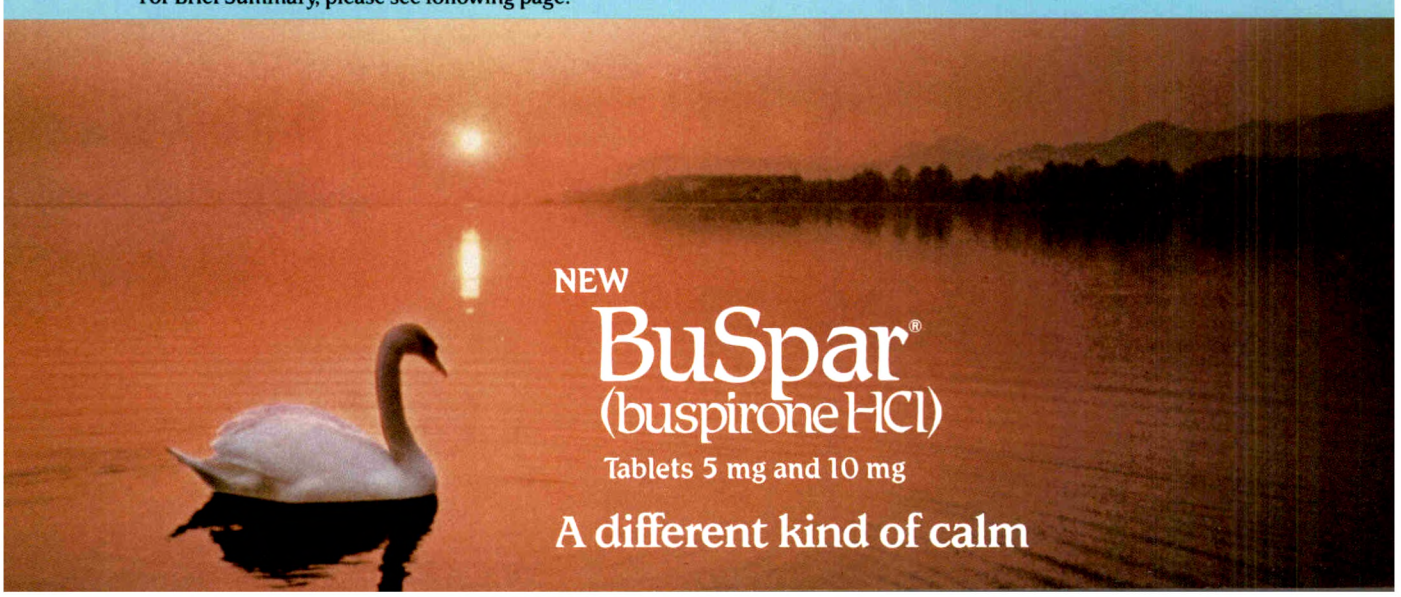
- Withdraw patients gradually from their prior treatment, especially those who have been using a CNS-depressant drug chronically.
- Recognize that rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug and its effective half-life of elimination.
- Remember that the withdrawal syndrome can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

BuSpar therapy may be discontinued by simply stopping administration

BuSpar...the first choice in anxiolytic therapy when:

- ☑ Treatment requires regular dosing for more than a few days
- ☑ Patient functioning is key to safe and successful treatment
- ☑ The potential for drug habituation, dependence, abuse, or a withdrawal syndrome is a concern

For Brief Summary, please see following page.





CONTRAINDICATIONS:
Hypersensitivity to buspirone.

WARNINGS:
Because BuSpar has no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.

PRECAUTIONS:
General—
Interference with cognitive and motor performance:
Studies indicate that BuSpar is less sedating than other anxiolytics and that it does not produce significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely.

While formal studies of the interaction of BuSpar with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug-dependent patients:
Because BuSpar does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with BuSpar, it is advisable to withdraw patients gradually, especially patients who have been using a CNS depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug, and its effective half-life of elimination.

The syndrome of withdrawal from sedative/hypnotic/anxiolytic drugs can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors:
Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported in some small fraction of buspirone-treated patients. The syndrome may be explained in several ways. For example, buspirone may increase central noradrenergic activity; alternatively, the effect may be attributable to dopaminergic effects (i.e., represent akathisia). Obviously, the question cannot be totally resolved at this point in time. Generally, long-term sequelae of any drug's use can be identified only after several years of marketing.

Information for Patients:
Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions:
Concomitant use with other CNS active drugs should be approached with caution. There is one report suggesting that the concomitant use of Desyrel® (trazodone) and BuSpar may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. In a similar study, attempting to replicate this finding, no interactive effect on hepatic transaminases was identified. Buspirone does not displace tightly bound drugs like phenytoin, propranolol and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy:
Teratogenic Effects:
Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers:
Administration to nursing women should be avoided if clinically possible.

Pediatric Use:
The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly:
No unusual adverse age-related phenomena have been identified in elderly patients.

Use in Patients with Impaired Hepatic or Renal Function:
Since buspirone is metabolized by the liver and excreted by the kidneys, its administration to patients with severe hepatic or renal impairment cannot be recommended.

ADVERSE REACTIONS (See also Precautions):
Commonly Observed:
The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness, nausea, headache, nervousness, light-headedness and excitement.

Associated with Discontinuation of Treatment:
The more common events causing discontinuation included central nervous system disturbances (3.4%)—primarily dizziness, insomnia, nervousness, drowsiness, and light-headed feeling; gastrointestinal disturbances (1.2%)—primarily nausea; and miscellaneous disturbances (1.1%)—primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials:
Adverse events that occurred at a frequency of 1% or more among 477 patients who received buspirone in four-week, controlled trials: **Cardiovascular:** tachycardia/palpitations 1%. **CNS:** dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, light-headedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. **EENT:** blurred vision 2%. **Gastrointestinal:** nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. **Musculoskeletal:** musculoskeletal aches/pains 1%. **Neurological:** numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. **Skin:** skin rash 1%. **Miscellaneous:** headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Pre-Marketing Evaluation:
The following list includes all other adverse events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under various conditions in well-controlled studies as well as open and uncontrolled clinical settings. The relative frequency of these adverse events is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. **Cardiovascular:** Frequent was nonspecific chest pain; infrequent were syncope, hypotension and hypertension; rare were cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy and bradycardia. **Central Nervous System:** Frequent were dream disturbances; infrequent were depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, disassociative reaction, hallucinations, suicidal ideation and seizures; rare were feelings of claustrophobia, cold intolerance, stupor, and slurred speech and psychosis. **EENT:** Frequent were tinnitus, sore throat and nasal congestion. Infrequent were redness and itching of the eyes, altered taste, altered smell, and conjunctivitis; rare were inner ear abnormality, eye pain, photophobia, and pressure on eyes. **Endocrine:** Rare were galactorrhea and thyroid abnormality. **Gastrointestinal:** Infrequent were flatulence, anorexia, increased appetite, salivation, irritable colon and rectal bleeding; rare was burning of the tongue. **Genitourinary:** Infrequent were urinary frequency, urinary hesitancy, menstrual irregularity and spotting, and dysuria; rare were amenorrhea, pelvic inflammatory disease, enuresis and nocturia. **Musculoskeletal:** Infrequent were muscle cramps, muscle spasms, rigid/stiff muscles, and arthralgias. **Neurological:** Infrequent were involuntary movements and slowed reaction time; rare was muscle weakness. **Respiratory:** Infrequent were hyperventilation, shortness of breath and chest congestion; rare was epistaxis. **Sexual Function:** Infrequent were decreased or increased libido; rare were delayed ejaculation and impotence. **Skin:** Infrequent were edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema and blisters; rare were acne and thinning of nails. **Clinical Laboratory:** Infrequent were increases in hepatic aminotransferases (SGOT, SGPT); rare were eosinophilia, leukopenia and thrombocytopenia. **Miscellaneous:** Infrequent were weight gain, fever, roaring sensation in the head, weight loss and malaise; rare were alcohol abuse, bleeding disturbance, loss of voice and hiccoughs.

DRUG ABUSE AND DEPENDENCE:
Controlled Substance Class:
BuSpar is not a controlled substance.

Physical and Psychological Dependence:
Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE:
Signs and Symptoms:
No deaths have been reported in humans either with deliberate or accidental overdosage. At doses approaching 375 mg/day, the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress.

Recommended Overdose Treatment:
General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

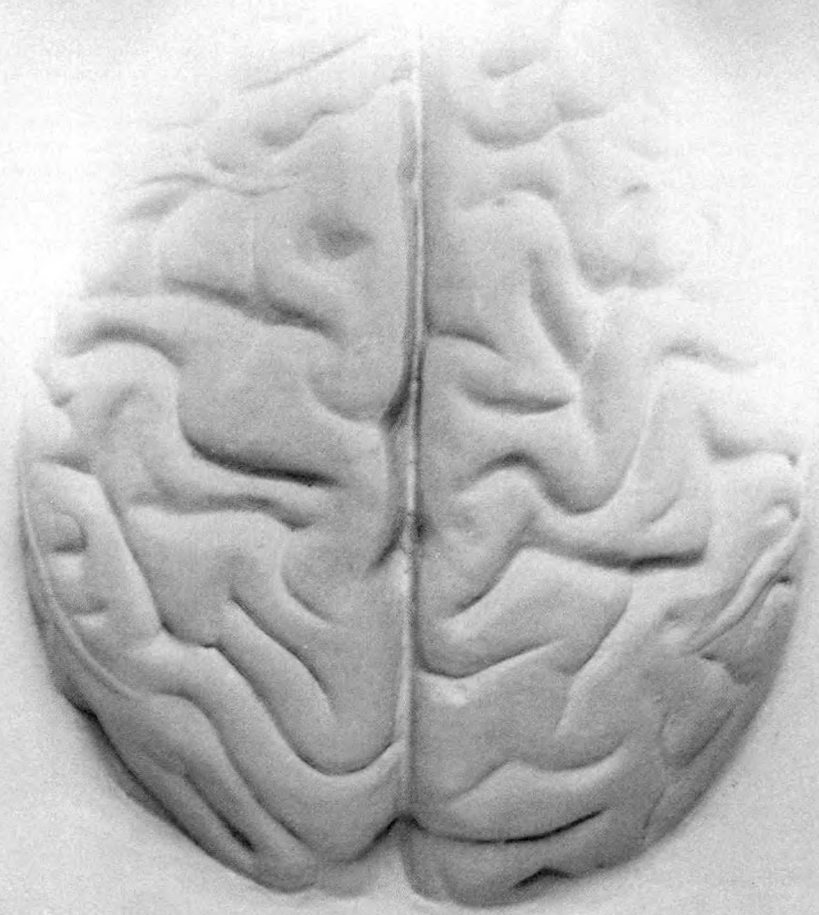
For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceutical Division Representative.

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2. Moskowitz H and Smiley A: Effects of chronically administered buspirone and diazepam on driving-related skills performance. *J Clin Psychiatry* 1982;43 (12, Sec 2):45-55.
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8. Griffith JD, *et al:* Investigation of the abuse liability of buspirone in alcohol-dependent patients. *Amer J Med* 1986;80 (3B):30-35.

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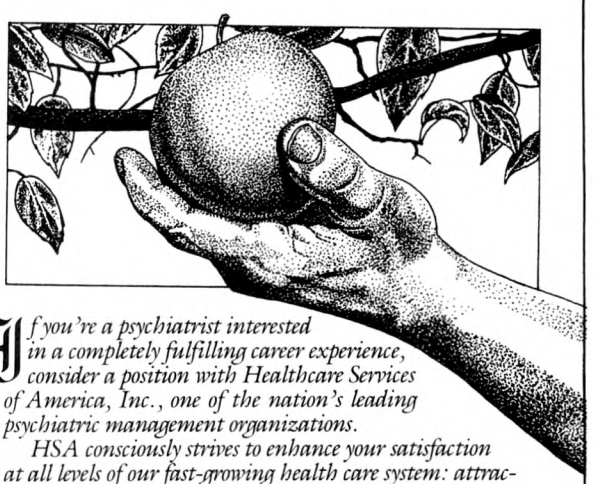
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PSYCHIATRY MEDICAL DIRECTOR POSITION

Northeastern Texas

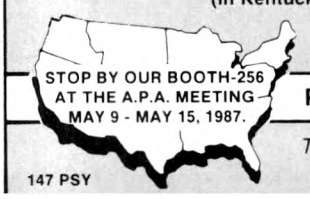
THE POSITION: Medical Director of a 40 bed Adult Program managed by Behavioral Medical Care (BMC), a nationwide psychiatric management firm. This is a salaried position for approximately 20 hours per week. The hospital will provide a competitive financial guarantee, office space, and assistance in setting up private practice.

THE HOSPITAL: The 448 bed full service medical center serves an area of 300,000 individuals living in counties in both Texas and Arkansas. There are three mental health programs managed by BMC in the hospital; a 40-bed adult program, a 24 bed adolescent program, and an adult chemical dependency program. The 150 active medical staff represent most specialties. There are six psychiatrists on active staff.

THE COMMUNITY: This stable community of 70,000 has two colleges nearby and strong public and private school systems. There are numerous cultural and recreational opportunities. The closest medical school is in Shreveport, Louisiana 70 miles away. It is a three hour drive to Dallas and a two hour drive to Little Rock, Arkansas.

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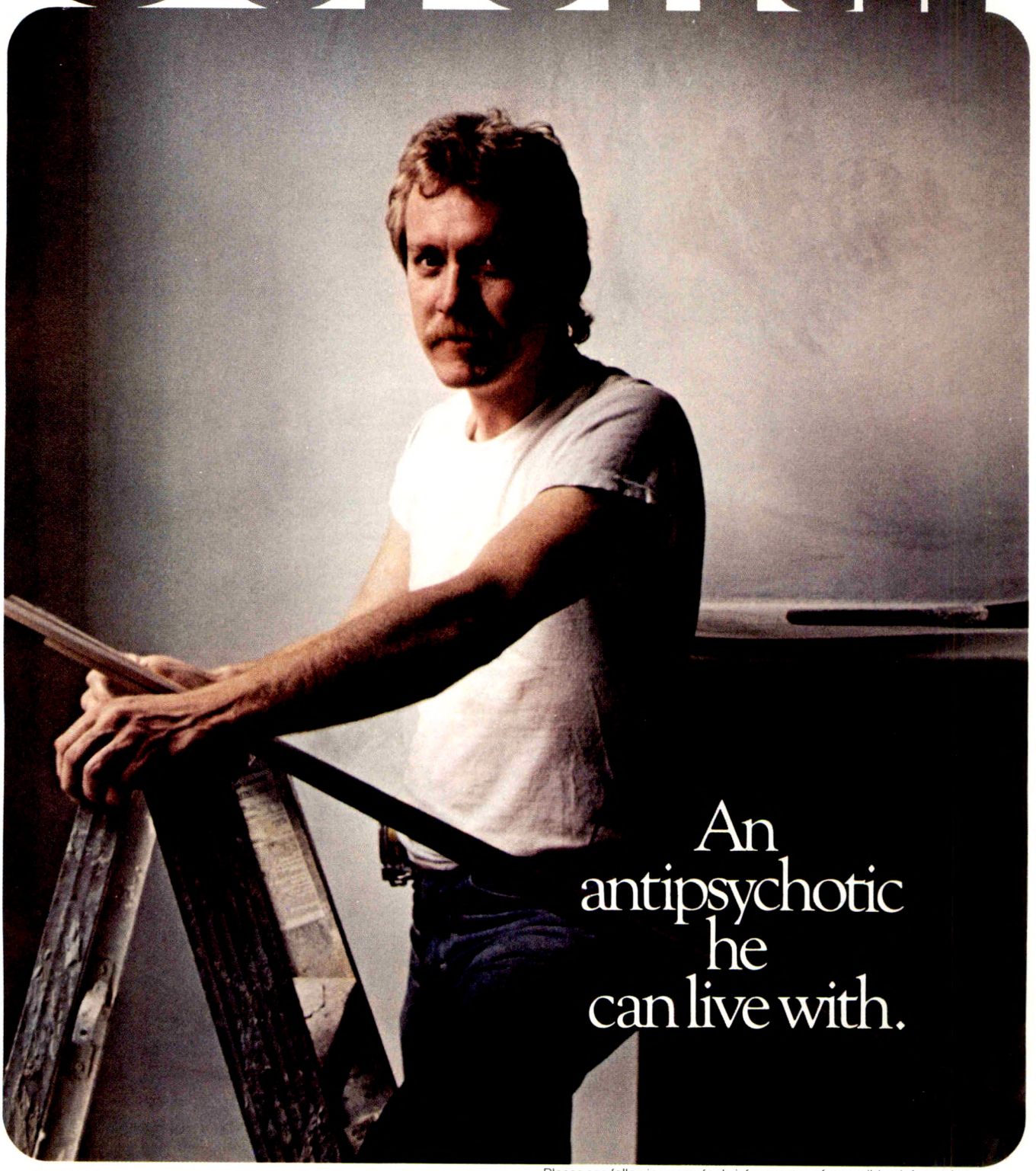
Voluntary Hospitals of America, Inc. (VHA)

147 PSY

(mesoridazine) Serentil®

as the besylate

IM/CONCENTRATE/TABLETS



An antipsychotic he can live with.

Please see following page for brief summary of prescribing information

Serentil® (mesoridazine) as the besylate

(mesoridazine) besylate tablets USP
(mesoridazine) besylate injection USP
(mesoridazine) besylate oral solution USP



Tablets: 10, 25, 50 and 100 mg | Concentrate: 25 mg/ml | Injectable: 1 ml (25 mg)

Brief Summary of Prescribing Information

Contraindications: As with other phenothiazines, Serentil® (mesoridazine), is contraindicated in severe central nervous system depression or comatose states from any cause. Serentil is contraindicated in individuals who have previously shown hypersensitivity to the drug.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness 1) that is known to respond to neuroleptic drugs, and 2) for which alternative, equally effective but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for Patients and Adverse Reactions).

Where patients are participating in activities requiring complete mental alertness (e.g. driving) it is advisable to administer the phenothiazines cautiously and to increase the dosage gradually.

Usage in Pregnancy: The safety of this drug in pregnancy has not been established; hence, it should be given only when the anticipated benefits to be derived from treatment exceed the possible risks to mother and fetus.

Usage in Children: The use of Serentil (mesoridazine) in children under 12 years of age is not recommended, because safe conditions for its use have not been established.

Attention should be paid to the fact that phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides.

Precautions: While ocular changes have not to date been related to Serentil® (mesoridazine), one should be aware that such changes have been seen with other drugs of this class.

Because of possible hypotensive effects, reserve parenteral administration for bedfast patients or for acute ambulatory cases, and keep patient lying down for at least one-half hour after injection.

Leukopenia and/or agranulocytosis have been attributed to phenothiazine therapy. A single case of transient granulocytopenia has been associated with Serentil. Since convulsive seizures have been reported, patients receiving anticonvulsant medication should be maintained on that regimen while receiving Serentil.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients: Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk.

Adverse Reactions: Drowsiness and hypotension were the most prevalent side effects encountered. Side effects tended to reach their maximum level of severity early with the exception of a few (rigidity and motoric effects) which occurred later in therapy.

With the exceptions of tremor and rigidity, adverse reactions were generally found among those patients who received relatively high doses early in treatment. Clinical data showed no tendency for the investigators to terminate treatment because of side effects.

Serentil® (mesoridazine) has demonstrated a remarkably low incidence of adverse reactions when compared with other phenothiazine compounds.

Central Nervous System: Drowsiness, Parkinson's syndrome, dizziness, weakness, tremor, restlessness, ataxia, dystonia, rigidity, slurring, akathisia, motoric reactions (opisthotonos) have been reported.

Autonomic Nervous System: Dry mouth, nausea and vomiting, fainting, stuffy nose, photophobia, constipation and blurred vision have occurred in some instances.

Genitourinary System: Inhibition of ejaculation, impotence, enuresis, incontinence have been reported.

Skin: Itching, rash, hypertrophic papillae of the tongue and angioneurotic edema have been reported.

Cardiovascular System: Hypotension and tachycardia have been reported. EKG changes have occurred in some instances (see Phenothiazine Derivatives: Cardiovascular Effects).

Phenothiazine Derivatives: It should be noted that efficacy, indications and untoward effects have varied with the different phenothiazines. The physician should be aware that the following have occurred with one or more phenothiazines and should be considered whenever one of these drugs is used:

Autonomic Reactions: Miosis, obstipation, anorexia, paralytic ileus.

Cutaneous Reactions: Erythema, exfoliative dermatitis, contact dermatitis.

Blood Dyscrasias: Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia.

Allergic Reactions: Fever, laryngeal edema, angioneurotic edema, asthma.

Hepatotoxicity: Jaundice, biliary stasis.

Cardiovascular Effects: Changes in the terminal portion of the electrocardiogram, including prolongation of the Q-T interval, lowering and inversion of the T wave and appearance of a wave tentatively identified as a bifid T or a U wave have been observed in some patients receiving the phenothiazine tranquilizers, including Serentil® (mesoridazine). To date, these appear to be due to altered repolarization and not related to myocardial damage. They appear to be reversible. While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, it should be noted that sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing characteristic electrocardiographic changes while taking the drug. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. Hypotension, rarely resulting in cardiac arrest, has been noted.

Extrapyramidal Symptoms: Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonos, oculogyric crises, tremor, muscular rigidity, akinesia.

Tardive Dyskinesia: Chronic use of neuroleptics may be associated with the development of tardive dyskinesia. The salient features of this syndrome are described in the **Warnings** section and below.

The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, face, mouth, lips, or jaw (e.g. protrusion of the tongue, puffing of cheeks, puckering of the mouth, chewing movements), trunk and extremities. The severity of the syndrome and the degree of impairment produced vary widely.

The syndrome may become clinically recognizable either during treatment, upon dosage reduction, or upon withdrawal of treatment. Movements may decrease in intensity and may disappear altogether if further treatment with neuroleptics is withheld. It is generally believed that reversibility is more likely after short rather than long-term neuroleptic exposure. Consequently, early detection of tardive dyskinesia is important. To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of neuroleptic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, for neuroleptic drugs may mask the signs of the syndrome.

Endocrine Disturbances: Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema. False positive pregnancy tests have been reported.

Urinary Disturbances: Retention, incontinence.

Others: Hyperpyrexia. Behavioral effects suggestive of a paradoxical reaction have been reported. These include excitement, bizarre dreams, aggravation of psychoses and toxic confusional states. More recently, a peculiar skin-eye syndrome has been recognized as a side effect following long-term treatment with phenothiazines. This reaction is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported. Systemic lupus erythematosus-like syndrome.

How Supplied:

Serentil® Tablets, for oral administration: 10 mg, 25 mg, 50 mg, and 100 mg mesoridazine (as the besylate). Bottles of 100.

Serentil® Ampuls, for intramuscular administration: 1 ml (25 mg mesoridazine (as the besylate)). Boxes of 20 and 100.

Serentil® Concentrate, for oral administration: Contains 25 mg mesoridazine (as the besylate) per ml, alcohol, USP, 0.61% by volume.

Immediate containers: Amber glass bottles of 4 fl oz (118 ml) packaged in cartons of 12 bottles, with an accompanying dropper graduated to deliver 10 mg, 25 mg and 50 mg of mesoridazine (as the besylate).

Consult package insert before prescribing.

SE-BPI-9/85

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EMERSON HOSPITAL

Concord, Massachusetts

DIRECTOR OF PSYCHIATRIC SERVICES

Emerson Hospital, in historic Concord, Massachusetts, is located only 20 miles from Boston. We are a 221-bed community acute care hospital with a 31-bed inpatient voluntary acute care unit serving a broad spectrum of psychiatric needs in a wide service area.

This is an established unit with an active medical staff and a variety of community referral sources. We are currently planning our move into a new major hospital wing with a complete unit dedicated to inpatient psychiatric services.

The Director should be willing to explore new organizational structures to address current and future clinical needs. The current level of organization includes a full professional staff, including an Assistant Director of Psychiatric Services.

We are looking for candidates who are Board Certified in Psychiatry who possess management experience in psychiatric administration and have some understanding of the practice of psychiatry in a community hospital setting. Candidates should be creative in their approach to the further development and growth of our psychiatric services. Emerson Hospital offers a competitive salary and benefits package.

Send curriculum vitae in complete confidence to:

Paul A. Reising, Jr., M.D.
Chairman, Search Committee
Emerson Hospital
Old Road to Nine Acre Corner
Concord, MA 01742

Emerson Hospital

Wednesday, May 13, 1987, 7:00 P.M.-10:00 P.M.
Chicago Hilton & Towers
International Ballroom North

The Department of Psychiatry, University of Texas Medical School, Houston, Texas

Presents

A Symposium on

THE REFRACTORY SCHIZOPHRENIC IS MANAGEMENT POSSIBLE?

CHAIRPERSON

LEO E. HOLLISTER, M.D., *Professor*
Department of Psychiatry, University of Texas, Houston, Texas

CO-CHAIRPERSON

JOHN KANE, M.D. *Director of Psychiatric Research and Professor of Psychiatry*
Hillside Hospital-Division of Long Island Jewish Medical Center, Glen Oaks, New York

Drug Induced Movement Disorders —Background Diagnosis
DONALD CALNE, M.D.
University British Columbia
Vancouver, B.C., Canada

Resistance to Pharmacologic & Psychosocial Interventions
PROFESSOR GERARD HOGARTY
Western State Psychiatric Institute
Pittsburgh, Pennsylvania

Neurologic Side Effects of Neuroleptic Drugs
JEFFREY LIEBERMAN, M.D.
Hillside Hospital-Division of
Long Island Jewish Medical Center
Glen Oaks, New York

Review of Current Therapies in Refractory Schizophrenia
LEO E. HOLLISTER, M.D.
University of Texas
Houston, Texas

New and Future Psychopharmacologic Therapies
HERBERT MELTZER, M.D.
Case Western Reserve University
Cleveland, Ohio

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Supported by a grant-in-aid from Sandoz Pharmaceuticals Corporation

The American Psychiatric Association designates this continuing medical education acivity for 3 credit hours in Category I of the Physician's Recognition Award of the American Medical Association and for the CME requirement of the APA.



*The total daily dosage of Sinequan may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg. This dose may be given at bedtime.

†**The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

For a brief summary of SINEQUAN prescribing information including adverse reactions, please see the following page of this advertisement.

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Antidepressant effectiveness
with once-a-day dosing*
SINEQUAN®
(doxepin HCl)
150-mg,† 100-mg, 75-mg, 50-mg,
25-mg, and 10-mg CAPSULES and
ORAL CONCENTRATE, 10-mg/ml,
120-ml (4-oz) bottles
Restores life's true colors
ROERIG
Pfizer
A division of Pfizer Pharmaceuticals

SINEQUAN® (doxepin HCl)

BRIEF SUMMARY
SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate
Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.
A. Signs and Symptoms
1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment
1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

ROERIG Pfizer

A division of Pfizer Pharmaceuticals
New York, New York 10017

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APRIL 1987

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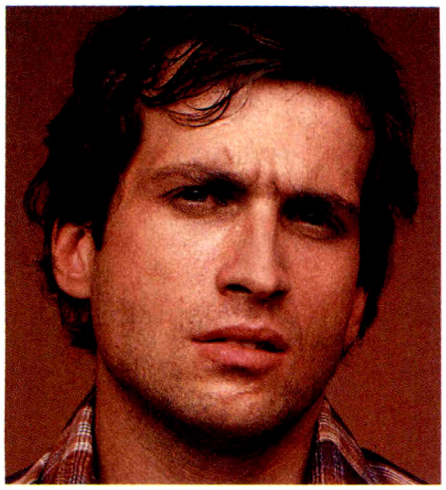
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For your schizophrenic patients

- Easily recognized color-coded tablets and tablet design
- Concentrate dropper calibrated in milligrams to facilitate dosage adjustment, as low as 1/2 mg.



Make sure they receive HALDOL® (HALOPERIDOL) and not a substitute



The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5 and 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis: the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia and tardive dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the syndrome may not develop. *Other CNS Effects*—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic Malignant Syndrome: As with other antipsychotic drugs, a symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported. Cardinal features of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. NMS is potentially fatal, requires intensive symptomatic treatment and immediate discontinuation of antipsychotic treatment. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported. *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

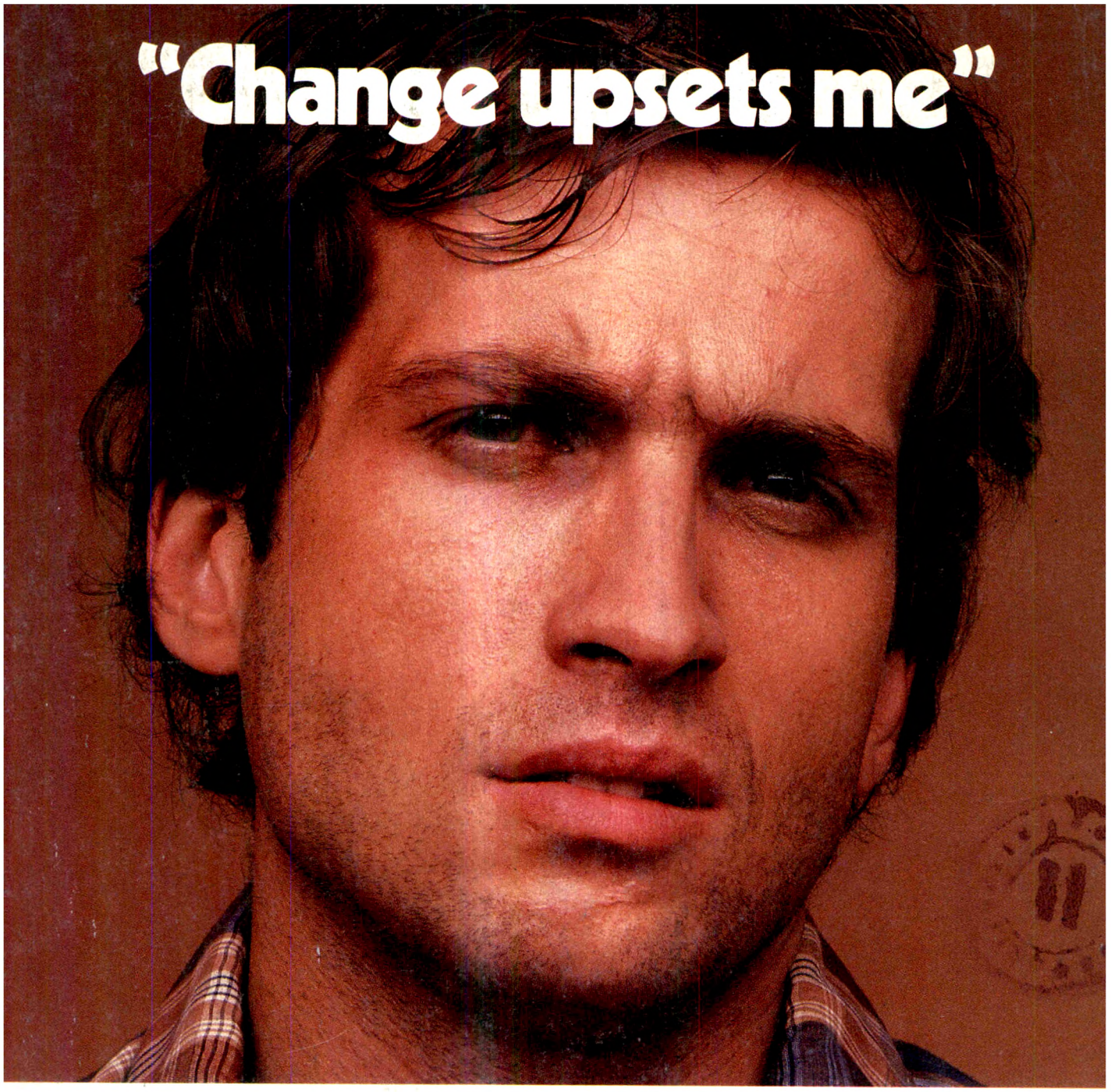
IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed. For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

11/10/86

McNEIL PHARMACEUTICAL
McNEIL AB INC. Spring House, PA 19477

795



Most patients with psychotic symptoms need a quiet, undemanding life that provides refuge from a confusing and overwhelming world.*[1]

You can help avoid one potentially stressful change by making sure your patients receive the unique HALDOL Tablet they can recognize.



HALDOL®
(HALOPERIDOL)

*Emphasis added.

1. Grinspoon L (ed). Care and treatment of schizoprenia—Part II, in *The Harvard Medical School Mental Health Letter* 1986; 3(1): 1.

Patient portrayed by professional model.

Please see brief summary of Prescribing Information on the preceding page.

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Do not substitute

McNEIL PHARMACEUTICAL
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THE AMERICAN JOURNAL OF PSYCHIATRY

Volume 144, Number 5 May 1987

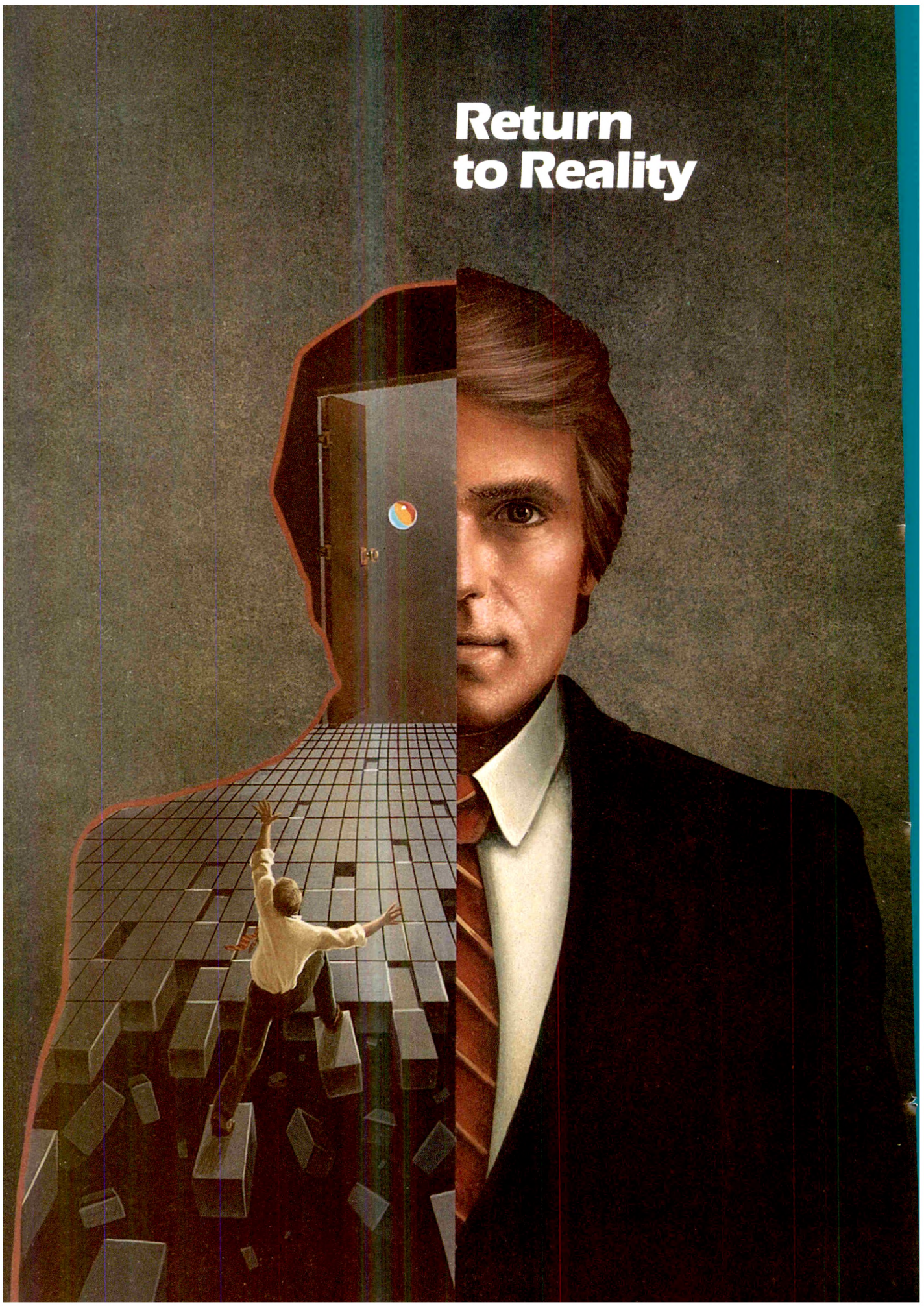
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Official Journal of the American Psychiatric Association


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to Reality

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Be sure you're the doctor...
always write
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Dispense as written.

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Helps Put the Chronic Schizophrenic Back in Touch

- ☐ Effectively controls psychotic target symptoms
- ☐ Apparently activates withdrawn, apathetic or detached patients
- ☐ Seldom causes excessive sedation
- ☐ Demonstrates a low risk of anticholinergic effects and hypotension
- ☐ Offers a convenient, economical b.i.d. dosage

'Stelazine' shares the increased risk of extrapyramidal symptoms associated with all high-potency neuroleptics. However, when encountered, these symptoms are generally readily controlled.

Stelazine®

brand of **trifluoperazine hydrochloride**

Before prescribing, see complete prescribing information in SK&F Co. literature or PDR. The following is a brief summary.

Contraindications: Comatose or greatly depressed states due to C.N.S. depressants, blood dyscrasias; bone marrow depression; liver damage.

Warnings: Tardive dyskinesia (TD) may develop in patients treated with neuroleptic (antipsychotic) drugs. The risk of TD and likelihood of irreversibility are thought to increase as duration of treatment and total cumulative neuroleptic dose increase. Much less commonly, the syndrome can develop after relatively brief treatment at low doses. There is no known treatment for TD, although it may remit if neuroleptics are withdrawn. Neuroleptic treatment may suppress signs and symptoms of the syndrome and thereby mask the underlying disease process. To minimize risk of TD, generally reserve chronic neuroleptic treatment for patients who suffer from chronic illness that responds to neuroleptics and for whom alternative, effective, less harmful treatments are not available or appropriate. In patients requiring chronic treatment, the minimal effective dose and shortest duration of treatment should be sought. Periodically reassess need for continued treatment. If signs and symptoms of TD appear, discontinuation of neuroleptics should be considered. (See PRECAUTIONS.)

Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

Patients with a history of long-term therapy with 'Stelazine' and/or other neuroleptics should be evaluated periodically for possible dosage adjustment or discontinuance of drug therapy. Neuroleptic drugs cause elevated prolactin levels that persist during chronic use. Since approximately one-third of human breast cancers are prolactin-dependent in vitro, this elevation is of potential importance if neuroleptic drug use is contemplated in a patient with a previously detected breast cancer. However, clinical and epidemiologic studies to date have not shown an association between the chronic use of neuroleptic drugs and mammary tumorigenesis. Use cautiously in persons who will be exposed to extreme heat.

Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

Adverse Reactions: Drowsiness, dizziness, skin reactions, rash, dry mouth, insomnia, amenorrhea, fatigue, muscular weakness, anorexia, lactation, blurred vision. Neuromuscular (extrapyramidal) reactions: motor restlessness, dystonias, pseudo-parkinsonism, tardive dyskinesia, and a variant, tardive dystonia.

Other adverse reactions reported with Stelazine (trifluoperazine HCl, SK&F) or other phenothiazines: Some adverse effects are more frequent or intense in specific disorders (e.g., mitral insufficiency or pheochromocytoma).

Grand mal and petit mal convulsions, particularly in the presence, or with history, of EEG abnormalities; altered cerebrospinal fluid proteins; cerebral edema; prolongation and intensification of the action of C.N.S. depressants, atropine, heat, and organophosphorus insecticides; nasal congestion, headache, nausea, constipation, obstipation, adynamic ileus, ejaculatory disorders/impotence, priapism, atonic colon, urinary retention, miosis and mydriasis; reactivation of psychotic processes, catatonic-like states, hypotension (sometimes fatal); cardiac arrest; leukopenia, eosinophilia, pancytopenia, agranulocytosis, thrombocytopenic purpura, hemolytic anemia, aplastic anemia, jaundice, biliary stasis, hyperglycemia, hypoglycemia, glycosuria, menstrual irregularities, galactorrhea, gynecomastia, false positive pregnancy tests, photosensitivity, itching, erythema, urticaria, eczema up to exfoliative dermatitis, asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions, peripheral edema; reversed epinephrine effect; hyperpyrexia; mild fever after large I.M. doses; increased appetite; increased weight; a systemic lupus erythematosus-like syndrome; pigmentary retinopathy; with prolonged administration of substantial doses, skin pigmentation, epithelial keratopathy, and lenticular and corneal deposits; neuroleptic malignant syndrome, which may be fatal; EKG changes—particularly nonspecific, usually reversible Q and T wave distortions—have been observed. Temporary nausea, vomiting, dizziness, and tremulousness may follow abrupt cessation of high-dose therapy. NOTE: Sudden death in patients taking phenothiazines (apparently due to cardiac arrest or asphyxia due to failure of cough reflex) has been reported.

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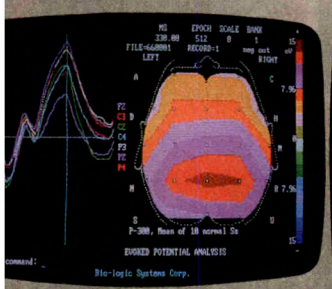
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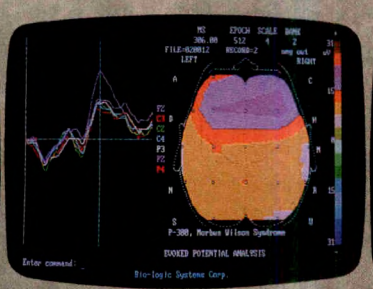
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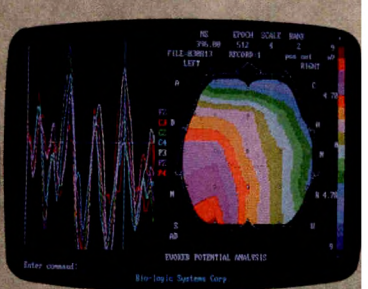
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P-300 of patient with Morbus Wilson Syndrome



FFT of EEG (EC), Morbus Wilson Syndrome



P-300 of patient with Alzheimer's Disease

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The American Journal of Psychiatry, ISSN 0002-953X, is published monthly by the American Psychiatric Association, 1400 K Street, N.W., Washington, DC 20005. Subscriptions: U.S. $50.00 per year, Canada and foreign $65.00; single issues: U.S. $7.00, Canada and foreign $8.00.

Business communications, changes of address, and questions about subscriptions from APA members should be directed to the Division of Member Services: (202) 682-6090. Communications from nonmember subscribers should be directed to the Circulation Department: (202) 682-6158. Authors who wish to contact the *Journal* editorial office should call (202) 682-6020.

Business Management: Nancy Frey, Director, Periodicals Services; Laura G. Abedi, Advertising Production Manager: (202) 682-6154; Beth Prester, Director, Circulation; Karen Loper, Promotion Manager; Jackie Coleman, Fulfillment Manager.

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Type set by Byrd PrePress, 5408 Port Royal Road, Springfield, VA 22151. Printed by Dartmouth Printing Company, 69 Lyme Road, Hanover, NH 03755.

Second-class postage paid at Washington, DC, and additional mailing offices. POSTMASTER: Send address changes to Circulation Department, American Psychiatric Association, 1400 K Street, N.W., Washington, DC 20005.

Indexed in *Abstracts for Social Workers, Biological Abstracts, Chemical Abstracts, Chicago Psychoanalytic Literature Index, Cumulative Index to Nursing Literature, Excerpta Medica, Hospital Literature Index, Index Medicus, International Nursing Index, Nutrition Abstracts, Psychological Abstracts, Science Citation Index,* and *Social Sciences Index.*

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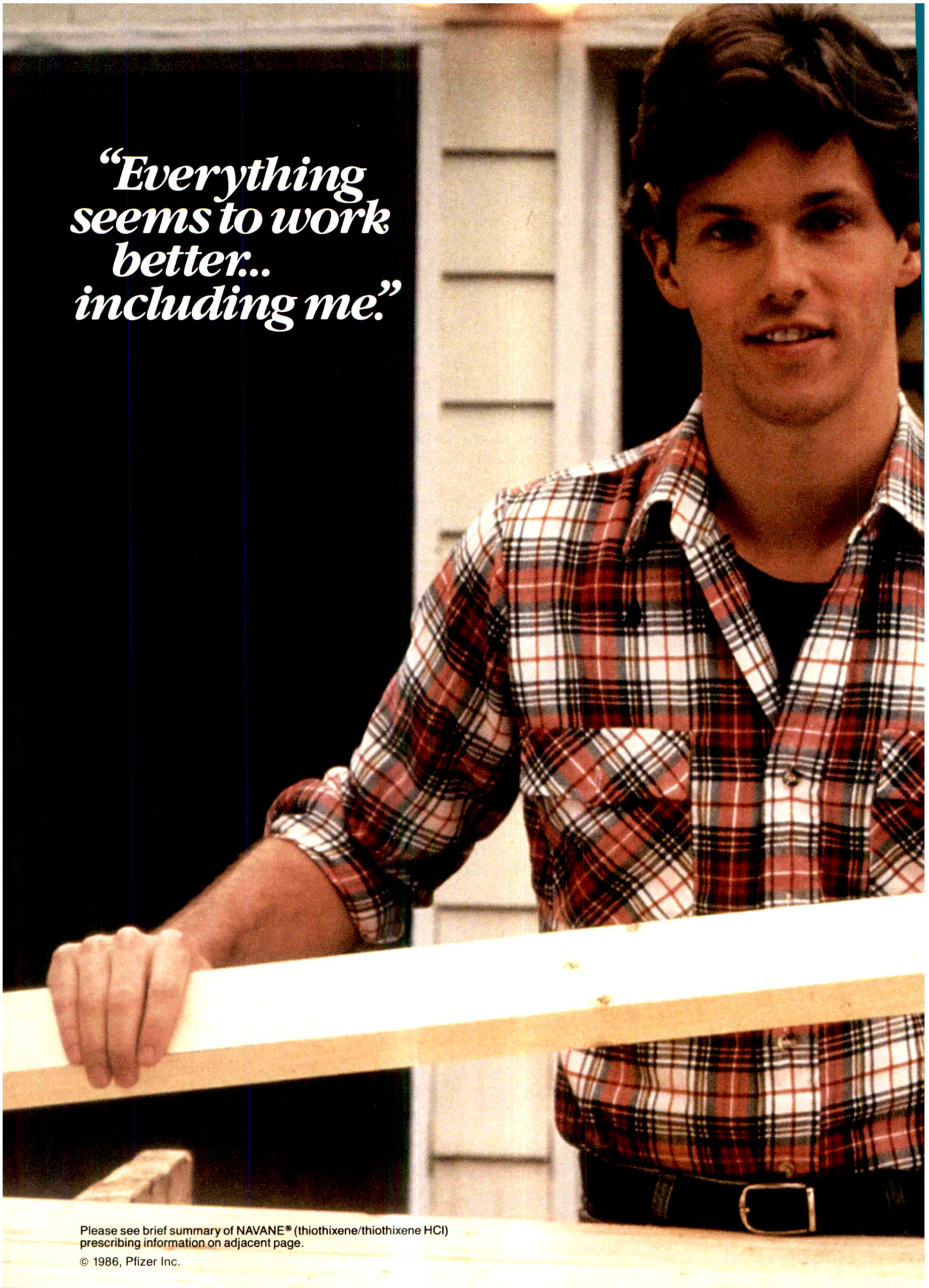
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References: **1** Bressler B, Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. **2** DiMascio A, Demirgian E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. **3** DiMascio A, Demirgian E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association..Washington, DC, May 3-6, 1971. **4** Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients, in Lehmann HE, Ban TA (eds): *The Thioxanthenes: Modern Problems of Pharmacopsychiatry.* Basel, Switzerland, S Karger, 1969, vol 2, pp 45-52. **5** Dillenkoffer RL, Gallant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented as a Scientific Exhibit at The 125th Annual Meeting of The American Psychiatric Association, Dallas, May 1-4, 1972. **6** Data available on request from Roerig.

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Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treament, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the section on Adverse Reactions.)

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypotension occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of blood pressure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thiothixene). These changes are usually reversible and frequently disappear on continued Navane therapy. The incidence of these changes is lower than that observed with some phenothiazines. The clinical significance of these changes is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of Navane therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, but less than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been noted with Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infrequently.

Hyperreflexia has been reported in infants delivered from mothers having received structurally related drugs.

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospinal fluid abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported. Management of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute symptoms may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be managed by reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in some patients on long term therapy or may occur after drug therapy has been discontinued.The risk seems to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities.

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing basis. It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome. If this or any other presentation of the syndrome is observed, the clinician should consider possible discontinuation of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have been infrequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane have been reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, which are usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associated with agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have been reported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Navane, exfoliative dermatitis and contact dermatitis (in nursing personnel) have been reported with certain phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a small percentage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the discontinuation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gynecomastia, hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, increased salivation, and impotence have occurred infequently with Navane therapy. Phenothiazines have been associated with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appetite and weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine therapy and the occurrence of a systemic lupus erythematosus-like syndrome.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenothiazine derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failure of the cough reflex. In others, the cause could not be determined nor could it be established that death was due to phenothiazine administration.

Dosage and Administration: Dosage of Navane should be individually adjusted depending on the chronicity and severity of the condition. In general, small doses should be used initially and gradually increased to the optimal effective level, based on patient response.

Some patients have been successfully maintained on once-a-day Navane therapy.

Usage in children under 12 years of age is not recommended because safe conditions for its use have not been established.

Navane Intramuscular Solution: Navane For Injection—When more rapid control and treatment of acute behavior is desirable, the intramuscular form of Navane may be indicated. It is also of benefit where the very nature of the patient's symptomatology, whether acute or chronic, renders oral administration impractical or even impossible.

For treatment of acute symptomatology or in patients unable or unwilling to take oral medication, the usual dose is 4 mg of Navane intramuscular administered 2 to 4 times daily. Dosage may be increased or decreased depending on response. Most patients are controlled on a total daily dosage of 16 to 20 mg. The maximum recommended dosage is 30 mg/day. An oral form should supplant the injectable form as soon as possible. It may be necessary to adjust the dosage when changing from the intramuscular to oral dosage forms. Dosage recommendations for Navane (thiothixene) Capsules and Concentrate appear in the following paragraphs.

Navane Capsules: Navane Concentrate—In milder conditions, an initial dose of 2 mg three times daily. If indicated, a subsequent increase to 15 mg/day total daily dose is often effective.

In more severe conditions, an initial dose of 5 mg twice daily.

The usual optimal dose is 20 to 30 mg daily. If indicated, an increase to 60 mg/day total daily dose is often effective. Exceeding a total daily dose of 60 mg rarely increases the beneficial response.

Overdosage: Manifestations include muscular twitching, drowsiness, and dizziness. Symptoms of gross overdosage may include CNS depression, rigidity, weakness, torticollis, tremor, salivation, dysphagia, hypotension, disturbances of gait, or coma.

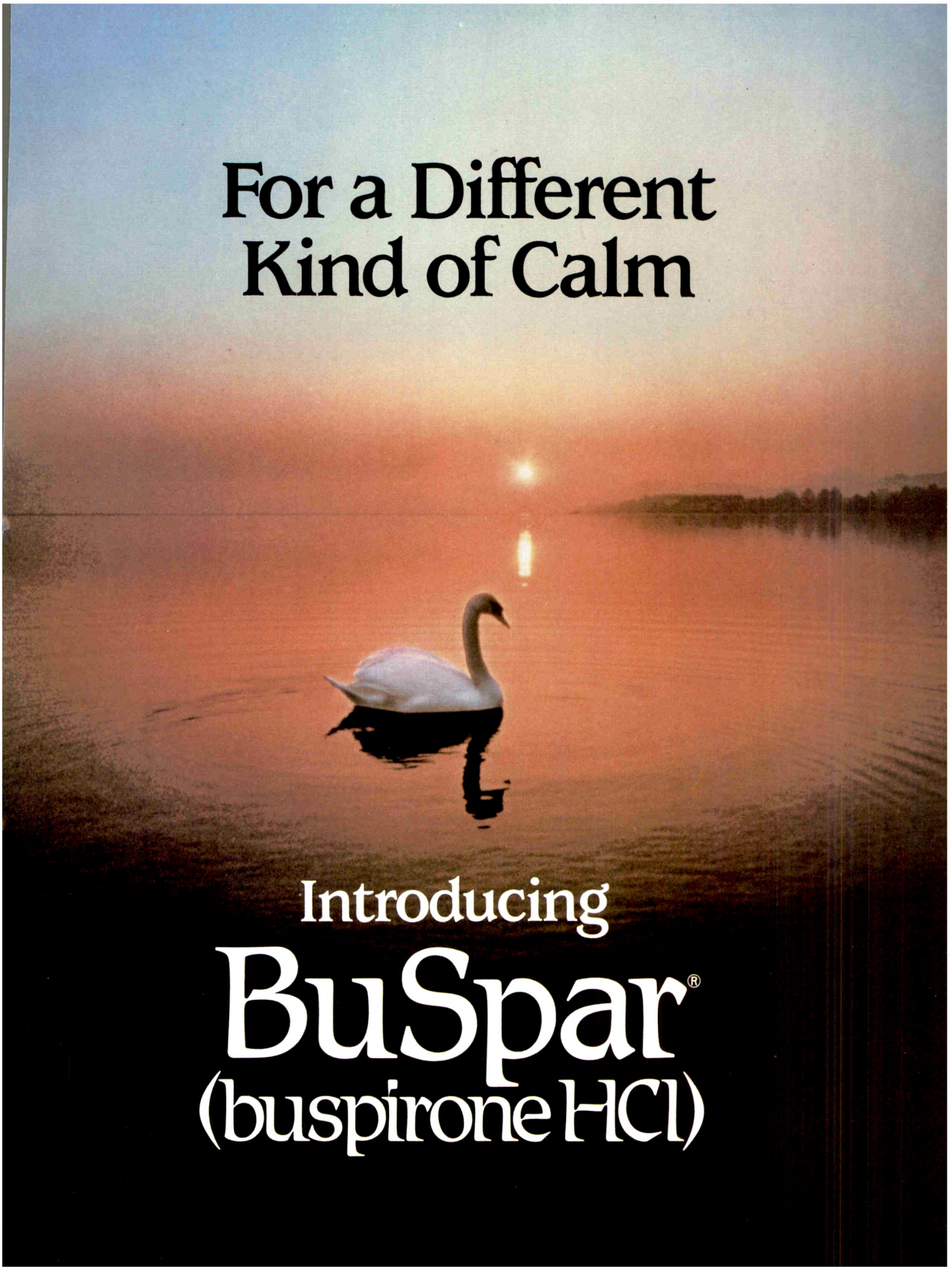
Treatment: Essentially is symptomatic and supportive. For Navane oral, early gastric lavage is helpful. For Navane oral and Intramuscular, keep patient under careful observation and maintain an open airway, since involvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overdosage. If hypotension occurs, the standard measures for managing circulatory shock should be used (I.V. fluids and/or vasoconstrictors.)

If a vasoconstrictor is needed, levarterenol and phenylephrine are the most suitable drugs. Other pressor agents, including epinephrine, are not recommended, since phenothiazine derivatives may reverse the usual pressor action of these agents and cause further lowering of the blood pressure.

If CNS depression is present and specific therapy is indicated, recommended stimulants include amphetamine, dextroamphetamine, or caffeine and sodium benzoate. Stimulants that may cause convulsions (e.g. picrotoxin or pentylenetetrazol) should be avoided. Extrapyramidal symptoms may be treated with antiparkinson drugs.

There are no data on the use of peritoneal or hemodialysis, but they are known to be of little value in phenothiazine intoxication.

ROERIG Pfizer
A division of Pfizer Pharmaceuticals
New York, New York 10017


For a Different
Kind of Calm
Introducing
BuSpar®
(buspirone HCl)

Mead Johnson
Pharmaceuticals
Introduces

BuSpar®
Tablets
5 mg and 10 mg

(buspirone HCl)

A different kind of calm

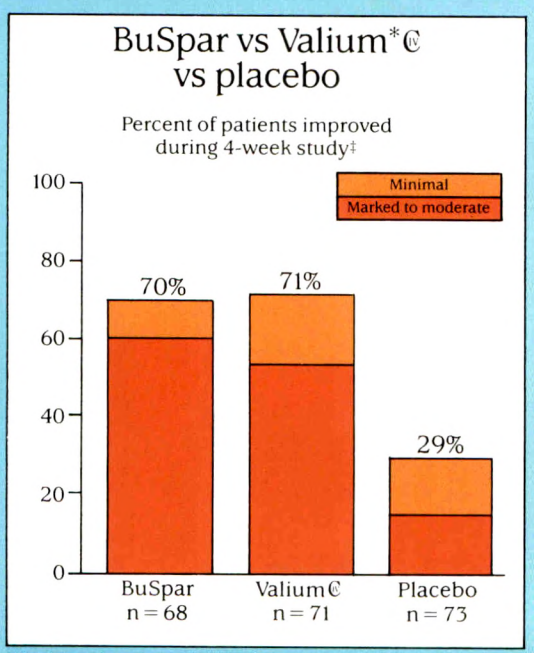
BuSpar—the first anxiolytic without CNS-depressant activity—has broken the connection between efficacy and unwanted sedative effects.

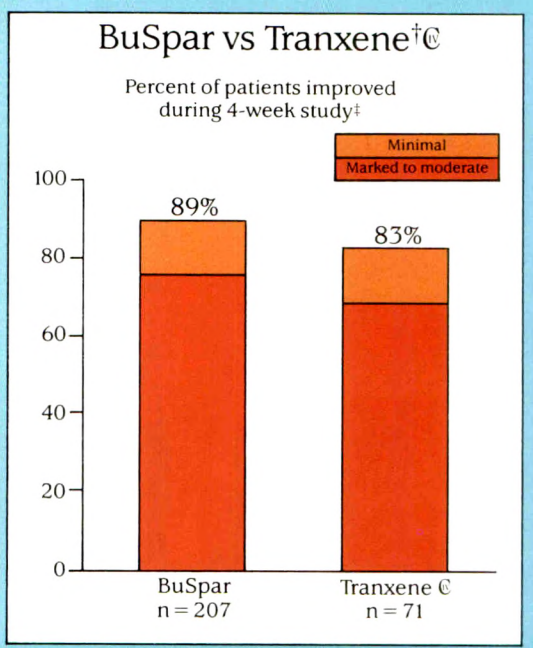
BuSpar gradually and comfortably provides relief of anxious symptoms—but produces no more drowsiness, motor impairment, or interaction with alcohol than does placebo.[1,2,3]

Furthermore, in clinical studies, BuSpar exhibited no apparent abuse liability, and no withdrawal syndrome has been reported at the end of therapy.[4,5]

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Proven anxiolytic effectiveness over a 4-week course of therapy[6,7]



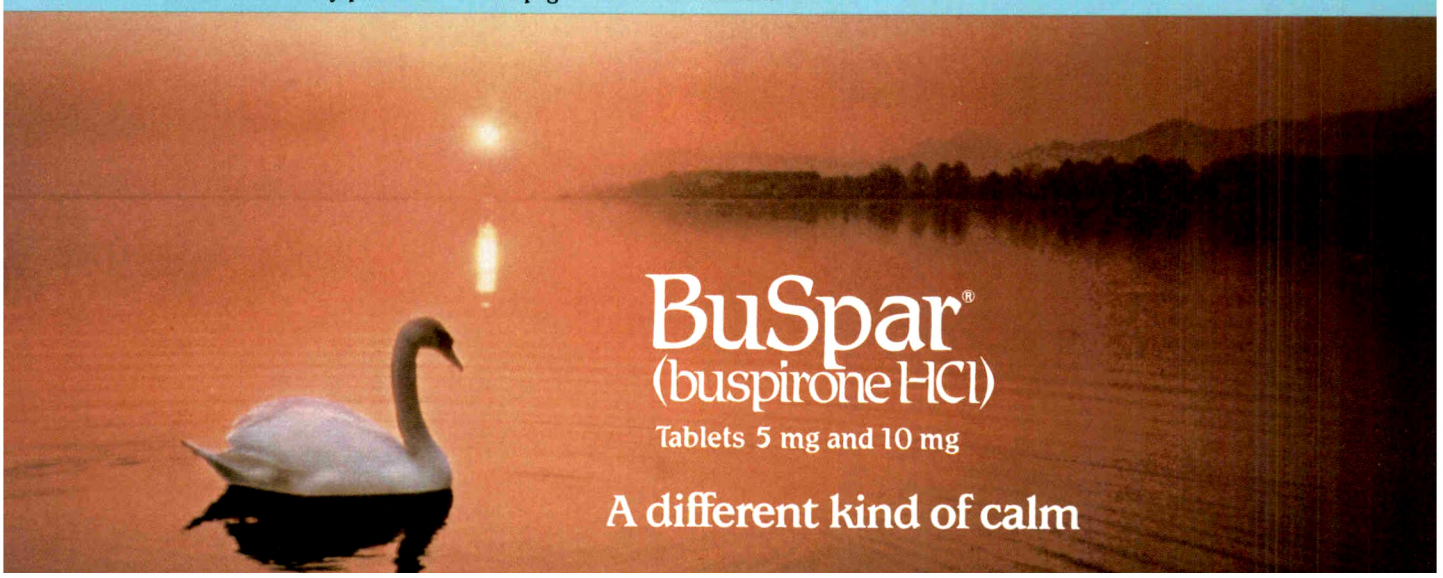


*Registered trademark of Hoffmann-La Roche Inc for diazepam.
†Registered trademark of Abbott Pharmaceuticals, Inc for clorazepate.
‡Physician's assessment of global improvement.

Extensive clinical trials have shown that BuSpar produces impressive results over a four-week course of therapy. In comparative trials with Valium and Tranxene, 70% to 89% of patients receiving BuSpar were judged by their physicians to be improved at the end of therapy. Significant improvement was noted in a wide range of anxiety-related symptoms such as anxious mood, depressed mood,* and cardiovascular and gastrointestinal complaints.

*BuSpar is not indicated for the treatment of primary depressive disorder.

For Brief Summary, please see the last page of this advertisement.



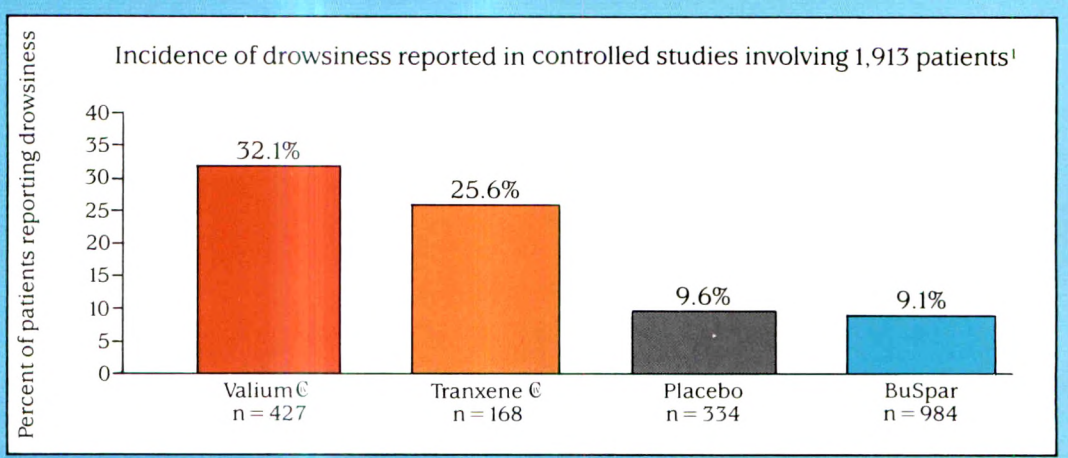
BuSpar®
Tablets
5 mg and 10 mg

(buspirone HCl)

Anxiolytic efficacy without CNS-depressant activity

Incidence of drowsiness no greater than placebo

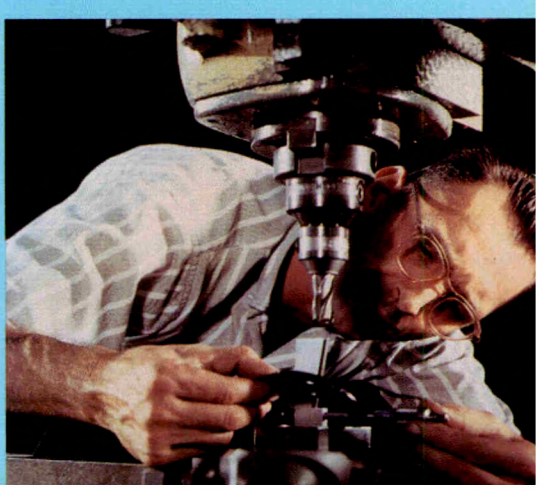
Because BuSpar does not replace symptoms with sedation, patients are alert and aware as well as anxiety-free during their waking hours.[1]



No impairment of motor skills

Controlled studies show that, unlike diazepam, BuSpar did not interfere with driving skills in normal subjects.[2]

NOTE: Patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.





No potentiation of the effects of alcohol

A controlled study in normal subjects showed that, unlike lorazepam, BuSpar did not augment the effects of alcohol.*[3]

No apparent abuse liability

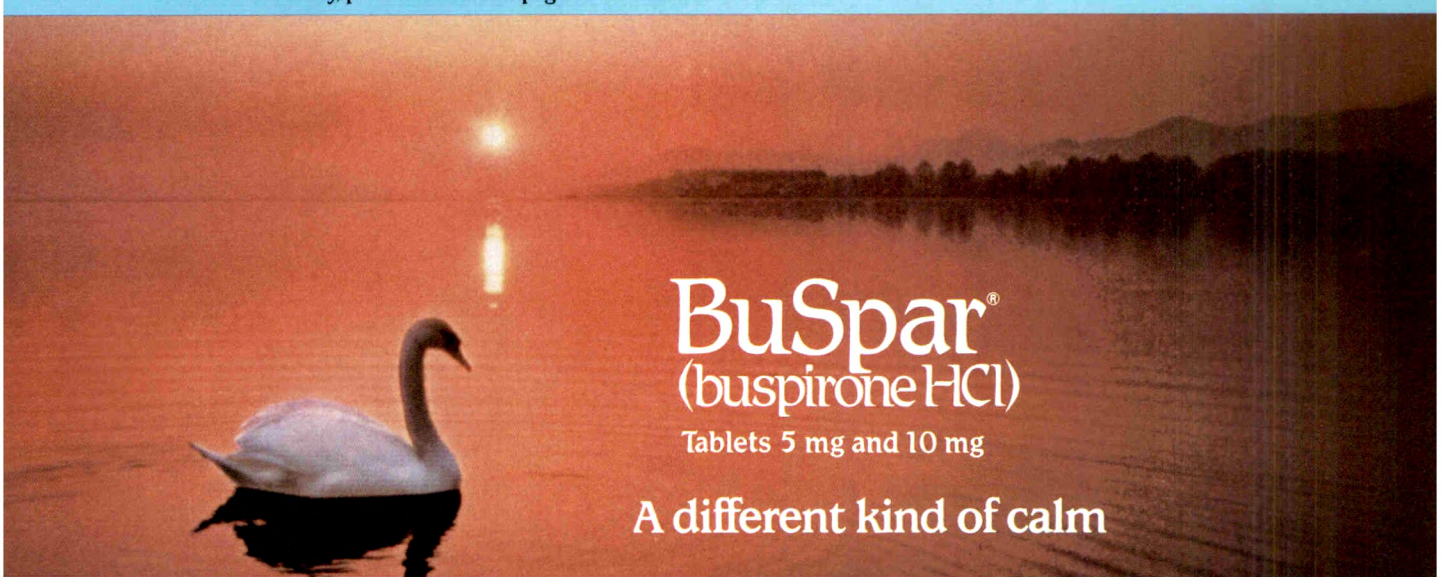
Extensive preclinical information and clinical data from studies in two populations, recreational users of sedatives and alcohol-dependent patients, demonstrate that BuSpar does not have the characteristics of common substances of abuse. Therefore, BuSpar is not a controlled substance.[4,8]

Well tolerated...with a low incidence of troublesome side effects

The most commonly observed adverse effects in controlled trials were dizziness (12%), nausea (8%), headache (6%), nervousness (5%), light-headedness (3%), and excitement (2%).

*While formal studies of the interaction of BuSpar with alcohol indicate that BuSpar does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and BuSpar.

For Brief Summary, please see the last page of this advertisement.



BuSpar®
Tablets
5 mg and 10 mg

(buspirone HCl)

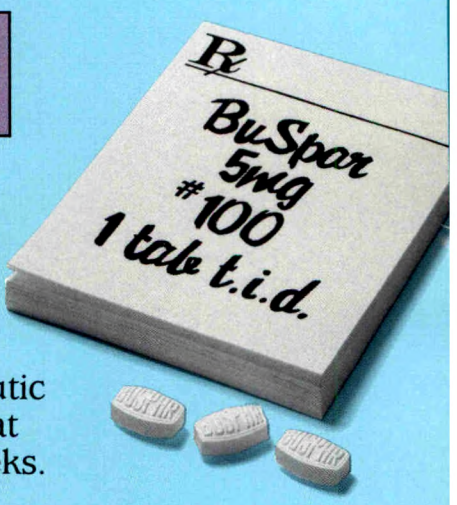
Subtle onset of effect

BuSpar relieves the symptoms of anxiety gradually and steadily. Generally, improvement will be noticeable within the first 7-10 days.

Prescribing recommendations

Initial dosage—5 mg t.i.d.

Week 1	5 mg	5 mg	5 mg



Dosage adjustment—5 mg/day increments, every 2-3 days, as needed, up to 60 mg/day.

Optimal daily dose—20-30 mg in divided doses, in most patients.

Length of therapy—To achieve full therapeutic benefit from BuSpar, it is recommended that treatment be prescribed for at least 3-4 weeks.

At the end of therapy

BuSpar therapy may be discontinued by simply stopping administration.

BuSpar is <u>not</u> a controlled substance.

Patient selection

BuSpar will <u>not</u> block the benzodiazepine withdrawal syndrome...therefore, the best candidates for BuSpar are those not currently taking benzodiazepines.

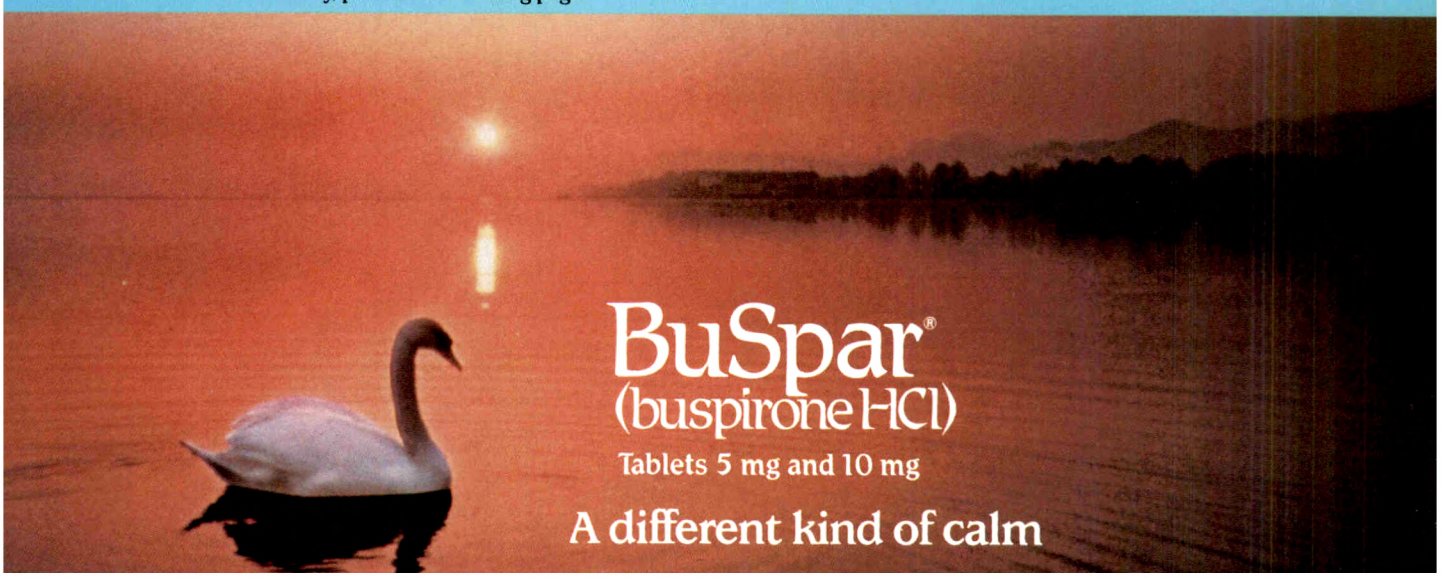
If you elect to switch a patient from a benzodiazepine to BuSpar:

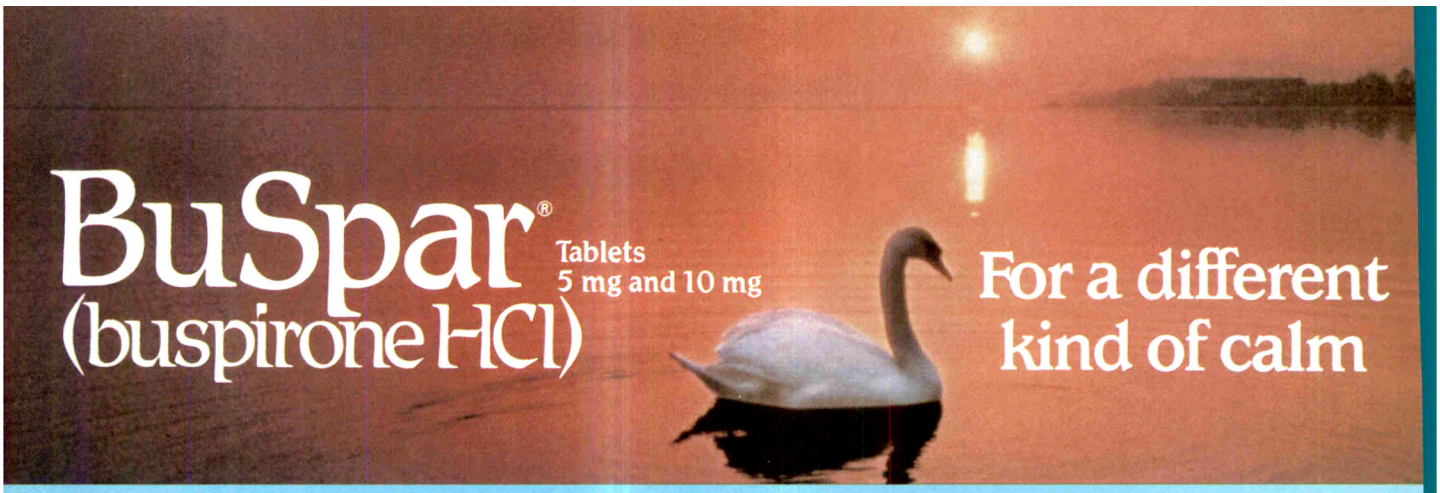
1. Carefully and completely withdraw the patient from the benzodiazepine according to the benzodiazepine manufacturer's instructions before initiating BuSpar therapy.
2. Remember that benzodiazepine withdrawal symptoms, such as irritability, anxiety, agitation, insomnia, sweating, and sometimes even seizures, may occur over varying time periods after discontinuation.

BuSpar...the first choice in anxiolytic therapy when:

- ☑ Treatment requires regular dosing for more than a few days
- ☑ Patient functioning is key to safe and successful treatment
- ☑ The potential for drug habituation, dependence, abuse, or a withdrawal syndrome is a concern

For Brief Summary, please see following page.





CONTRAINDICATIONS:
Hypersensitivity to buspirone.

WARNINGS:
The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. There have been reports of the occurrence of elevated blood pressure when BuSpar has been added to a regimen including an MAOI. Therefore, it is recommended that BuSpar not be used concomitantly with an MAOI.

Because BuSpar has no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.

PRECAUTIONS:
General—
Interference with cognitive and motor performance:
Studies indicate that BuSpar is less sedating than other anxiolytics and that it does not produce significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely.

While formal studies of the interaction of BuSpar with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug-dependent patients:
Because BuSpar does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with BuSpar, it is advisable to withdraw patients gradually, especially patients who have been using a CNS depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug, and its effective half-life of elimination.

The syndrome of withdrawal from sedative/hypnotic/anxiolytic drugs can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors:
Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported in some small fraction of buspirone-treated patients. The syndrome may be explained in several ways. For example, buspirone may increase central noradrenergic activity; alternatively, the effect may be attributable to dopaminergic effects (i.e., represent akathisia). Obviously, the question cannot be totally resolved at this point in time. Generally, long-term sequelae of any drug's use can be identified only after several years of marketing.

Information for Patients:
Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions:
Concomitant use with other CNS active drugs should be approached with caution. There is one report suggesting that the concomitant use of Desyrel® (trazodone) and BuSpar may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. In a similar study, attempting to replicate this finding, no interactive effect on hepatic transaminases was identified. Buspirone does not displace tightly bound drugs like phenytoin, propranolol and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. (See WARNINGS)

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy:
Teratogenic Effects:
Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers:
Administration to nursing women should be avoided if clinically possible.

Pediatric Use:
The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly:
No unusual adverse age-related phenomena have been identified in elderly patients.

Use in Patients with Impaired Hepatic or Renal Function:
Since buspirone is metabolized by the liver and excreted by the kidneys, its administration to patients with severe hepatic or renal impairment cannot be recommended.

ADVERSE REACTIONS (See also Precautions):
Commonly Observed:
The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness, nausea, headache, nervousness, light-headedness and excitement.

Associated with Discontinuation of Treatment:
The more common events causing discontinuation included central nervous system disturbances (3.4%)—primarily dizziness, insomnia, nervousness, drowsiness, and light-headed feeling; gastrointestinal disturbances (1.2%)—primarily nausea; and miscellaneous disturbances (1.1%)—primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials:
Adverse events that occurred at a frequency of 1% or more among 477 patients who received buspirone in four-week, controlled trials: **Cardiovascular:** tachycardia/palpitations 1%. **CNS:** dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, light-headedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. **EENT:** blurred vision 2%. **Gastrointestinal:** nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. **Musculoskeletal:** musculoskeletal aches/pains 1%. **Neurological:** numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. **Skin:** skin rash 1%. **Miscellaneous:** headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Pre-Marketing Evaluation:
The following list includes all other adverse events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under various conditions in well-controlled studies as well as open and uncontrolled clinical settings. The relative frequency of these adverse events is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. **Cardiovascular:** Frequent was nonspecific chest pain; infrequent were syncope, hypotension and hypertension; rare were cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy and bradycardia. **Central Nervous System:** Frequent were dream disturbances; infrequent were depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, disassociative reaction, hallucinations, suicidal ideation and seizures; rare were feelings of claustrophobia, cold intolerance, stupor, and slurred speech and psychosis. **EENT:** Frequent were tinnitus, sore throat and nasal congestion. Infrequent were redness and itching of the eyes, altered taste, altered smell, and conjunctivitis; rare were inner ear abnormality, eye pain, photophobia, and pressure on eyes. **Endocrine:** Rare were galactorrhea and thyroid abnormality. **Gastrointestinal:** Infrequent were flatulence, anorexia, increased appetite, salivation, irritable colon and rectal bleeding; rare was burning of the tongue. **Genitourinary:** Infrequent were urinary frequency, urinary hesitancy, menstrual irregularity and spotting, and dysuria; rare were amenorrhea, pelvic inflammatory disease, enuresis and nocturia. **Musculoskeletal:** Infrequent were muscle cramps, muscle spasms, rigid/stiff muscles, and arthralgias. **Neurological:** Infrequent were involuntary movements and slowed reaction time; rare was muscle weakness. **Respiratory:** Infrequent were hyperventilation, shortness of breath and chest congestion; rare was epistaxis. **Sexual Function:** Infrequent were decreased or increased libido; rare were delayed ejaculation and impotence. **Skin:** Infrequent were edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema and blisters; rare were acne and thinning of nails. **Clinical Laboratory:** Infrequent were increases in hepatic aminotransferases (SGOT, SGPT); rare were eosinophilia, leukopenia and thrombocytopenia. **Miscellaneous:** Infrequent were weight gain, fever, roaring sensation in the head, weight loss and malaise; rare were alcohol abuse, bleeding disturbance, loss of voice and hiccoughs.

DRUG ABUSE AND DEPENDENCE:
Controlled Substance Class:
BuSpar is not a controlled substance.

Physical and Psychological Dependence:
Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE:
Signs and Symptoms:
No deaths have been reported in humans either with deliberate or accidental overdosage. At doses approaching 375 mg/day, the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress.

Recommended Overdose Treatment:
General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceutical Division Representative.

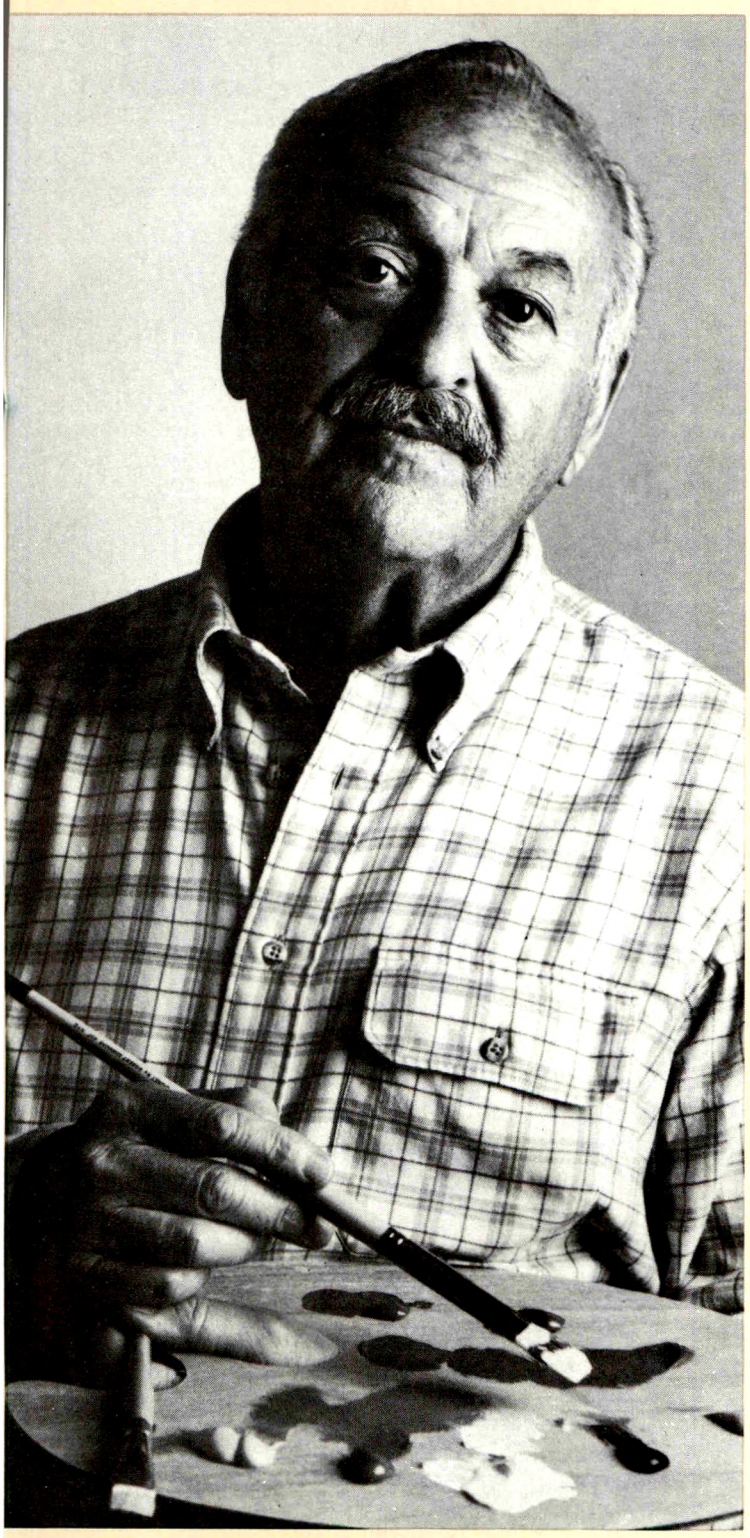
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Mead Johnson
PHARMACEUTICALS
Bristol-Myers U.S. Pharmaceutical
and Nutritional Group
Evansville, Indiana 47721 U S A

MJL3-4856

MOBAN® molindone HCl achieved rapid control of severe symptomatology in just five days ...with only one 25-mg tablet/day.



Professional model was used for this photograph.
Case history on file at Du Pont Pharmaceuticals.

The efficacy and safety of MOBAN was recently demonstrated in a violent geriatric patient with delusional thinking and paranoid ideation. Taken to a hospital by force, the patient had assaulted his bedridden wife because he believed she was having an affair with a younger man.

Results:

- Admitted as an involuntary patient, MOBAN succeeded in reducing his symptoms sufficiently to permit transfer to a psychogeriatric ward after just five days of treatment.
- Dosage was subsequently reduced to only 15 mg/day.
- After four weeks, there was no evidence of delusional thinking, paranoia or hallucinatory behavior.
- Even without anticholinergic medication, there were no side effects.

Conclusion:

MOBAN was effective and safe at the low doses usually recommended for geriatrics who require major tranquilizers. Clinical experience with other geriatrics has also demonstrated efficacy with a rare incidence of significant hypotension, weight gain or impotence.

MOBAN is available exclusively from Du Pont.

Please see following page for prescribing information.

Patient-friendly Psychiatric Products

Du Pont Pharmaceuticals

DU PONT

MOBAN® (molindone hydrochloride)

INDICATIONS: MOBAN is indicated for the management of the manifestations of psychotic disorders. The antipsychotic efficacy of MOBAN was established in clinical studies which enrolled newly hospitalized and chronically hospitalized, acutely ill, schizophrenic patients as subjects.

CONTRAINDICATIONS: Severe central nervous system depression, comatose states from any cause, and in patients with known hypersensitivity to the drug.

WARNINGS: Tardive Dyskinesia—This syndrome (potentially irreversible, involuntary, dyskinetic movements) may develop in patients treated with neuroleptic (antipsychotic) drugs. Prevalence appears highest among the elderly, especially women; it is impossible to predict which patients are likely to develop the syndrome. Both risk of syndrome development and likelihood of its becoming irreversible are believed to increase with duration of treatment and total cumulative dose; the syndrome can develop after brief treatment periods at low doses. There is no known treatment; partial or complete remission may occur if neuroleptic treatment is withdrawn. Neuroleptic treatment may supress or partially supress signs and symptoms of the syndrome and thereby mask the underlying disease process. Effect of symptomatic supression upon long-term course of the syndrome is unknown. Prescribe neuroleptics in a manner most likely to minimize the occurrence of tardive dyskinesia. Reserve chronic neuroleptic treatment for patients suffering from a chronic illness that is known to respond to neuroleptic drugs and for whom alternative treatments are not available or appropriate. In those requiring chronic treatment the smallest dose and shortest duration of treatment producing satisfactory clinical response should be sought. Need for treatment should be reassessed periodically. Consider discontinuing treatment if signs and symptoms of tardive dyskinesia appear; some patients may require treatment despite presence of the syndrome.

Usage in Pregnancy: Studies in pregnant patients have not been carried out. Animal reproductive studies have not demonstrated a teratogenic potential. Anticipated benefits must be weighed against the unknown risks to the fetus if used in pregnant patients.

Nursing Mothers: Data are not available on the content of MOBAN in the milk of nursing mothers.

Usage in Children: Use of MOBAN in children below the age of twelve years is not recommended because safe and effective conditions for its usage have not been established. MOBAN has not been shown effective in the management of behavioral complications in patients with mental retardation.

Sulfites Sensitivity: MOBAN Concentrate contains sodium metabisulfite, a sulfite that may cause allergic-type reactions (e.g. hives, itching, wheezing, anaphylaxis) in certain susceptible persons. Although the overall prevalence of sulfite sensitivity in the general population is probably low, it is seen more frequently in asthmatics or in atopic nonasthmatic persons.

PRECAUTIONS: Some patients may note drowsiness initially; advise against activities requiring mental alertness until response to the drug has been established. Increased activity has been noted in patients receiving MOBAN. Caution should be exercised where increased activity may be harmful. MOBAN does not lower the seizure threshold in experimental animals to the degree noted with more sedating antipsychotic drugs; in humans convulsive seizures have been reported in a few instances. This tablet preparation contains calcium sulfate as an excipient; calcium ions may interfere with the absorption of preparations containing phenytoin sodium and tetracyclines. MOBAN has an antiemetic effect in animals. A similar effect may occur in humans and may obscure signs of intestinal obstruction or brain tumor. Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

ADVERSE REACTIONS: CNS EFFECTS: Most frequently occurring effect is initial drowsiness that generally subsides with continued usage or lowering of the dose. Noted less frequently were depression, hyperactivity and euphoria.

Neurological—Extrapyramidal Reactions noted below may occur in susceptible individuals; usually reversible with appropriate management.

Akathisia: Motor restlessness may occur early.

Parkinson Syndrome: Akinesia, characterized by rigidity, immobility and reduction of voluntary movements and tremor, have been observed. Occurrence is less frequent than akathisia.

Dystonic Syndrome: Prolonged abnormal contractions of muscle groups occur infrequently. Symptoms may be managed by the addition of a synthetic antiparkinson agent (other than L-dopa), small doses of sedative drugs, and/or reduction in dosage.

Tardive Dyskinesia: Persistent and sometimes irreversible. See preceeding paragraph under "Warnings."

Autonomic Nervous System: Occasional blurring of vision, tachycardia, nausea, dry mouth and salivation. Urinary retention and constipation may occur, particularly if anticholinergic drugs are used to treat extrapyramidal symptoms.

Laboratory Tests: Rare reports of leucopenia and leucocytosis; treatment with MOBAN may continue if clinical symptoms are absent. Alterations of blood glucose, liver function tests, BUN, and red blood cells have not been considered clinically significant.

Metabolic and Endocrine Effects: Alteration of thyroid function has not been significant. Amenorrhea has been reported infrequently. Resumption of menses in previously amenorrheic women has been reported. Initially heavy menses may occur. Galactorrhea and gynecomastia have been reported infrequently. Increase in libido has been noted in some patients. Impotence has not been reported. Although both weight gain and weight loss have been in the direction of normal or ideal weight, excessive weight gain has not occurred with MOBAN.

Hepatic Effects: There have been rare reports of clinically significant alterations in liver function in association with MOBAN use.

Cardiovascular: Rare, transient, non-specific T wave changes have been reported on EKG. Association with a clinical syndrome has not been established. Rarely has significant hypotension been reported.

Ophthalmological: Lens opacities and pigmentary retinopathy have not been reported. In some patients phenothiazine-induced lenticular opacities have resolved following discontinuation of the phenothiazine while continuing therapy with MOBAN.

Skin: Early non-specific skin rash, probably of allergic origin, has occasionally been reported. Skin pigmentation has not been seen with MOBAN usage alone. MOBAN has certain pharmacological similarities to other antipsychotic agents. Because adverse reactions are often extensions of the pharmacological activity of a drug, all of the known pharmacological effects associated with other antipsychotic drugs should be kept in mind when MOBAN is used. Upon abrupt withdrawal after prolonged high dosage an abstinence syndrome has not been noted.

DOSAGE: Initial and maintenance doses of MOBAN should be individualized. See full prescribing information.

OVERDOSAGE: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

HOW SUPPLIED: Tablets: 5 mg, 10 mg, 25 mg, 50 mg and 100 mg in bottles of 100.

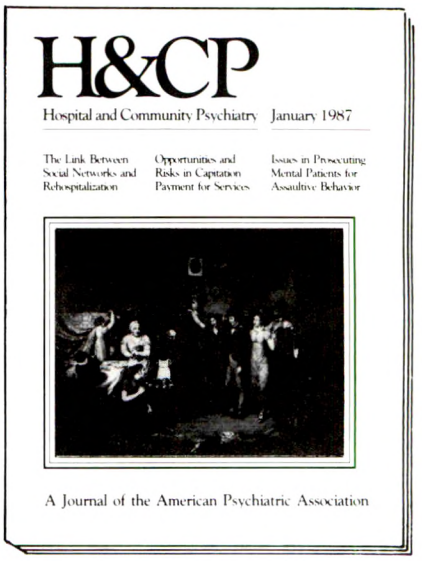
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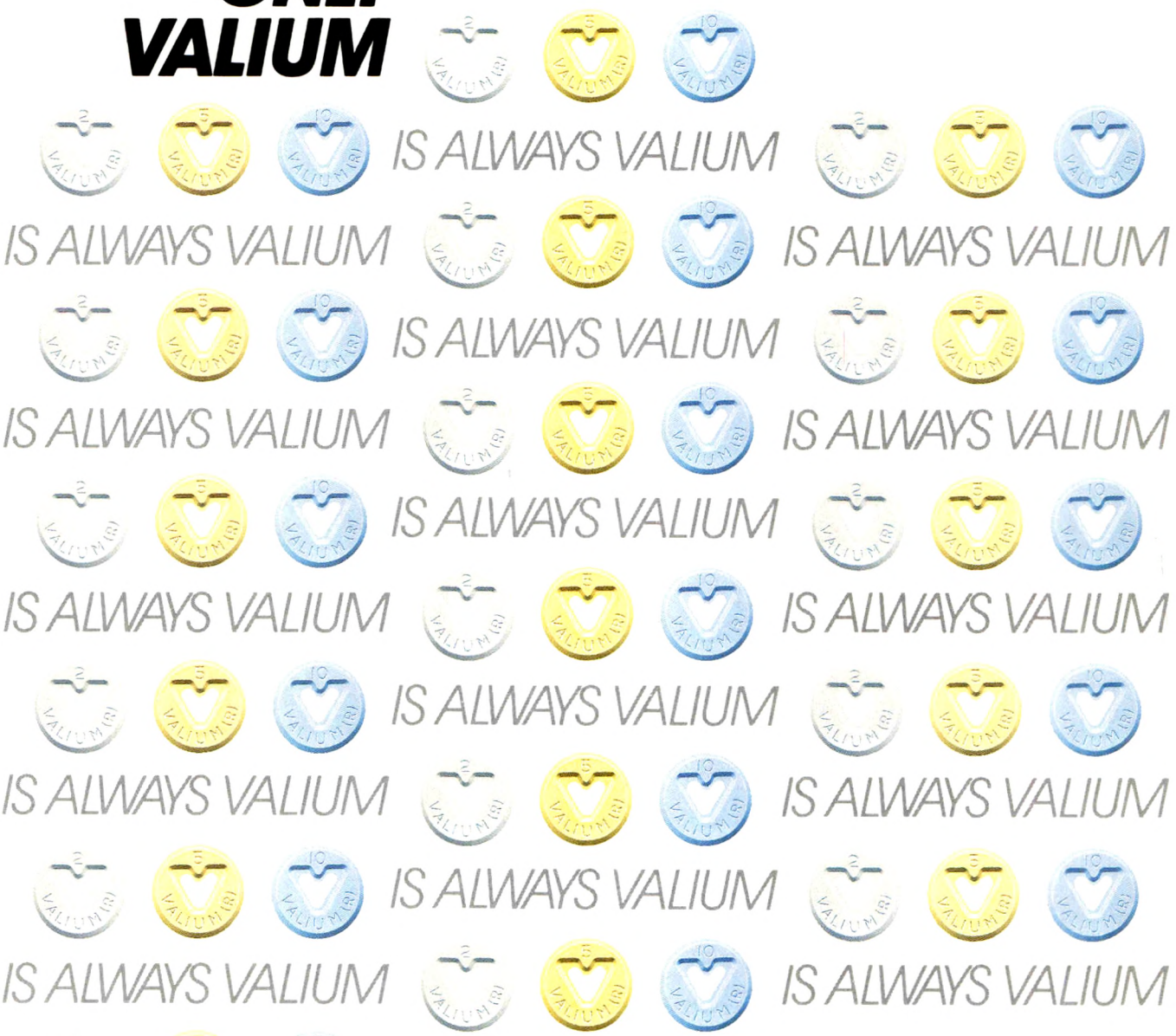
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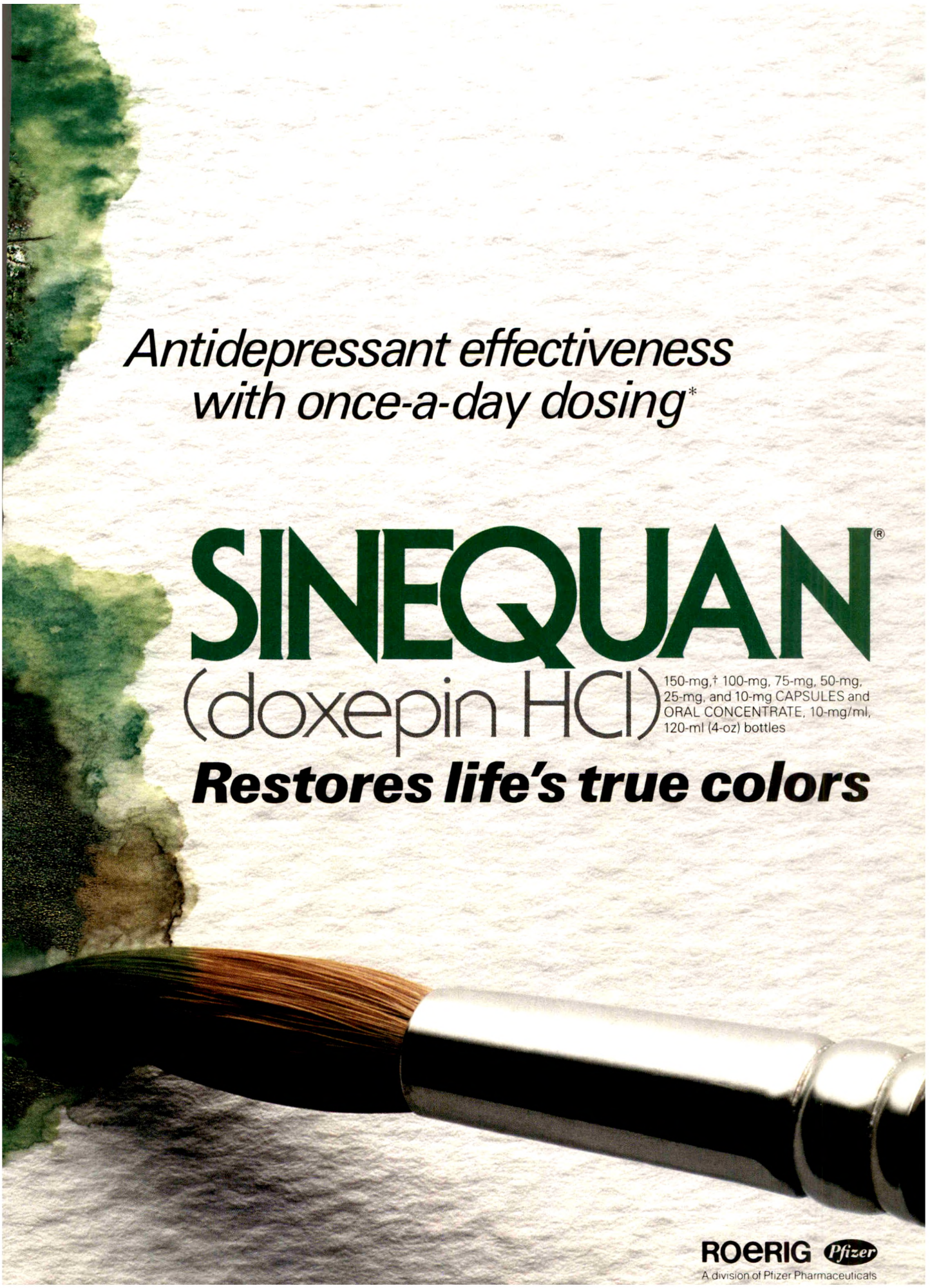


*The total daily dosage of Sinequan may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed, the maximum recommended dose is 150 mg. This dose may be given at bedtime.

†**The 150-mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

For a brief summary of SINEQUAN prescribing information including adverse reactions, please see the following page of this advertisement.

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Antidepressant effectiveness
with once-a-day dosing*
SINEQUAN®
(doxepin HCl)
150-mg,† 100-mg, 75-mg, 50-mg,
25-mg, and 10-mg CAPSULES and
ORAL CONCENTRATE, 10-mg/ml,
120-ml (4-oz) bottles
Restores life's true colors
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SINEQUAN® (doxepin HCl)

BRIEF SUMMARY
SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate
Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred.

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.
A. Signs and Symptoms
1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment
1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

More detailed professional information available on request.

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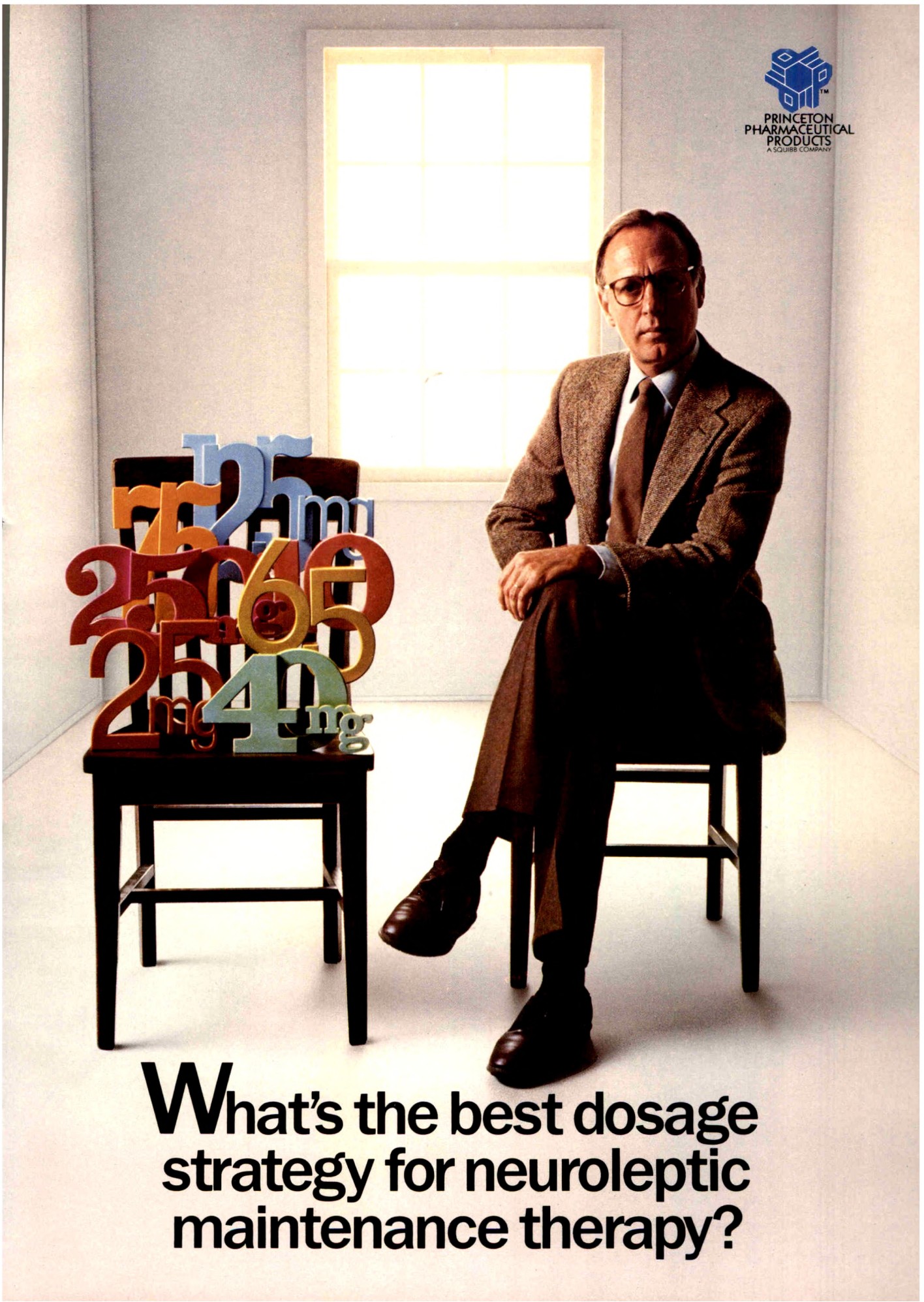
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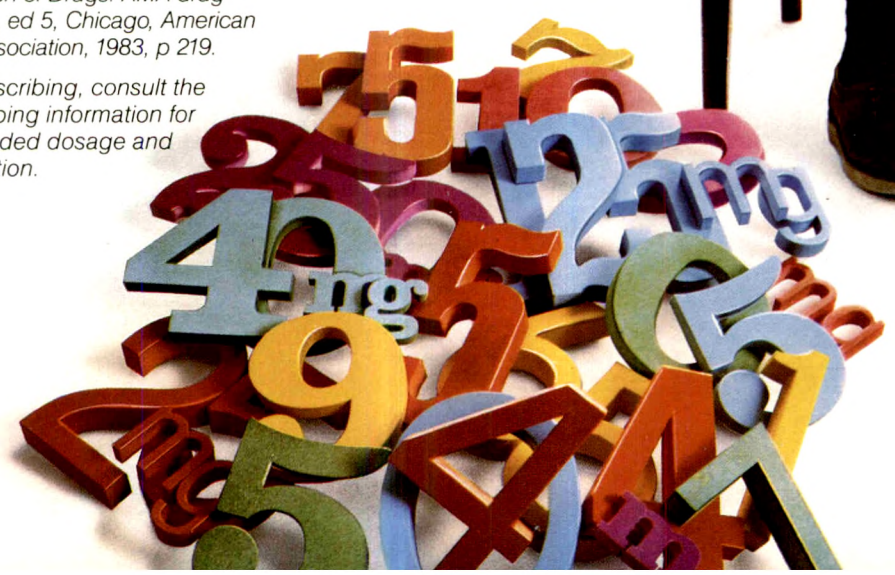
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†Before prescribing, consult the full prescribing information for recommended dosage and administration.



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5 mg/mL in bottles of 120 mL with calibrated dropper



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*Please check the substitution laws in your state.

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PROLIXIN DECANOATE*
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DESCRIPTION: Prolixin Tablets (Fluphenazine Hydrochloride Tablets USP) provide 1, 2.5, 5, or 10 mg fluphenazine hydrochloride per tablet. Prolixin 2.5, 5, and 10 mg tablets contain FD&C Yellow No. 5 (tartrazine). Prolixin Elixir (Fluphenazine Hydrochloride Elixir USP) provides 0.5 mg fluphenazine hydrochloride per mL (2.5 mg per 5 mL teaspoonful) with 14% alcohol by volume. Prolixin Oral Concentrate (Fluphenazine Hydrochloride Oral Solution*) provides 5 mg fluphenazine hydrochloride per mL, with 14%* alcohol by volume (exceeds the USP monograph 1.2% limit). Prolixin Injection (Fluphenazine Hydrochloride Injection USP) provides 2.5 mg fluphenazine hydrochloride per mL; it contains 0.1% methylparaben and 0.01% propylparaben as preservatives. Prolixin Decanoate (Fluphenazine Decanoate Injection) provides 25 mg fluphenazine decanoate per mL in a sesame oil vehicle with 1.2% (w/v) benzyl alcohol as preservative.

CONTRAINDICATIONS: In the presence of suspected or established subcortical brain damage. In patients who have a blood dyscrasia or liver damage, or who are receiving large doses of hypnotics, or who are comatose or severely depressed. In patients who have shown hypersensitivity to fluphenazine; cross-sensitivity to phenothiazine derivatives may occur. Fluphenazine Decanoate is not intended for use in children under 12.

WARNINGS: Tardive Dyskinesia—potentially irreversible, involuntary, dyskinetic movements may develop. This syndrome appears to be most prevalent among the elderly, especially women; however, prevalence estimates do not reliably predict, at the inception of neuroleptic treatment, those patients likely to develop the syndrome. It is unknown if neuroleptics differ in their potential to cause tardive dyskinesia. The risk of developing the syndrome and the likelihood of its irreversibility are believed to increase as duration of treatment and cumulative dose increase. Although uncommon, the syndrome can develop after brief treatment at low doses. There is no known treatment for tardive dyskinesia, although partial or complete remission may occur with withdrawal of the neuroleptic. Neuroleptic treatment may suppress signs and symptoms of the syndrome and may mask the underlying disease process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown. Neuroleptics should, thus, be prescribed with consideration for the potential of tardive dyskinesia. Chronic treatment should generally be reserved for patients with chronic illness that responds to neuroleptic drugs, and for whom alternative effective, less harmful treatments are *not* available or appropriate. Patients requiring chronic treatment should receive the smallest dose and shortest duration of treatment producing a satisfactory clinical response. Continuation of treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear, neuroleptic discontinuation should be considered. However, some patients may require continued treatment. (See PRECAUTIONS and ADVERSE REACTIONS.)

Mental and physical abilities required for driving a car or operating heavy machinery may be impaired by use of this drug. Potentiation of effects of alcohol may occur. Safety and efficacy in children have not been established because of inadequate experience in use in children. Severe adverse reactions, requiring immediate medical attention, may possibly occur.

Usage In Pregnancy: Safety for use during pregnancy has not been established; weigh possible hazards against potential benefits if administering any of these drugs to pregnant patients.

PRECAUTIONS: Caution must be exercised if another phenothiazine compound caused cholestatic jaundice, dermatoses or other allergic reactions because of the possibility of cross-sensitivity. Prolixin Tablets (Fluphenazine Hydrochloride Tablets USP) 2.5, 5, and 10 mg contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity. When psychotic patients on large doses of a phenothiazine drug are to undergo surgery, hypotensive phenomena should be watched for; less anesthetics or central nervous system depressants may be required. Because of added anticholinergic effects, fluphenazine may potentiate the effects of atropine.

Use fluphenazine cautiously in patients exposed to extreme heat or phosphorus insecticides; in patients with a history of convulsive disorders, since grand mal convulsions have occurred; and in patients with special medical disorders, such as mitral insufficiency or other cardiovascular diseases and pheochromocytoma. Bear in mind that with prolonged therapy there is the possibility of liver damage, pigmentary retinopathy, lenticular and corneal deposits, and development of irreversible dyskinesia.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Periodic checking of hepatic and renal functions and blood picture should be done. Monitor renal function of patients on long-term therapy; if BUN becomes abnormal, discontinue fluphenazine. "Silent pneumonias" are possible. Fluphenazine decanoate should be administered under the direction of a physician experienced in the clinical use of psychotropic drugs.

Information for Patients: It is likely that some patients exposed chronically to neuroleptics will develop tardive dyskinesia; full information should be given to all patients, if possible, who are candidates for chronic use. Informing patients and/or guardians must take into account clinical circumstances and patient competency.

Abrupt Withdrawal: In general, phenothiazines do not produce psychic dependence. However, gastritis, nausea and vomiting, dizziness, and tremulousness have been reported following abrupt cessation of high dose therapy; reports suggest that these symptoms can be reduced if concomitant antiparkinsonian agents are continued for several weeks after the phenothiazine is withdrawn.

ADVERSE REACTIONS: *Central Nervous System:* Extrapyramidal symptoms are most frequently reported. Most often these symptoms are reversible, but they may be persistent. They include pseudoparkinsonism, dystonia, dyskinesia, akathisia, oculogyric crises, opisthotonos, and hyperreflexia. Muscle rigidity sometimes accompanied by hyperthermia has been reported following use of fluphenazine decanoate. One can expect a higher incidence of such reactions with fluphenazine decanoate than with less potent piperazine derivatives or straight-chain phenothiazines. The incidence and severity of such reactions will depend more on individual patient sensitivity, but dosage level and patient age are also determinants. As these reactions may be alarming, the patient should be forewarned and reassured. These reactions can usually be controlled by administration of an antiparkinsonian drug such as benztropine mesylate and by subsequent reduction in dosage.

Tardive Dyskinesia: See WARNINGS. Characterized by involuntary choreoathetoid movements involving tongue, face, mouth, lips, or jaw (e.g., tongue protrusion, puffing cheeks, puckering mouth, chewing movements), trunk and extremities. Severity and degree of impairment vary widely. May become clinically recognizable either during treatment, dosage reduction, or treatment withdrawal. To facilitate early detection, reduce dosage periodically (if clinically possible) and observe for signs of the disorder, especially since neuroleptics may mask the signs of the syndrome.

References: 1. Baldessarini RJ: Drugs and the treatment of psychiatric disorders, in Gilman AG, Goodman LS (eds): The Pharmacological Basis of Therapeutics, ed 6. New York, Macmillan Publishing Co, Inc , 1980, p 415. **2.** Mason AS, Granacher RP: Clinical Handbook of Antipsychotic Drug Therapy. New York, Brunner/Mazel, 1980, pp 203, 221, 239.

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Please see brief summary continuing on following page.

Rare occurrences of neuroleptic malignant syndrome (NMS) have been reported in patients on neuroleptic therapy. The syndrome is characterized by hyperthermia, muscular rigidity, autonomic instability (labile blood pressure, tachycardia, diaphoresis), akinesia, and altered consciousness, sometimes progressing to stupor or coma. Leukocytosis, elevated CPK, liver function abnormalities, and acute renal failure may also occur. Neuroleptic therapy should be discontinued immediately and vigorous symptomatic treatment implemented since the syndrome is potentially fatal.

Phenothiazine derivatives have been known to cause restlessness, excitement, or bizarre dreams; reactivation or aggravation of psychotic processes may be encountered. If drowsiness or lethargy occurs, the dosage may need to be reduced. Dosages, far in excess of the recommended amounts, may induce a catatonic-like state.

Autonomic Nervous System: Hypertension and fluctuations in blood pressure have been reported. Although hypotension is rarely a problem, patients with pheochromocytoma, cerebral vascular or renal insufficiency, or a severe cardiac reserve deficiency such as mitral insufficiency appear to be particularly prone to this reaction and should be observed carefully. Supportive measures including intravenous vasopressor drugs should be instituted immediately should severe hypotension occur; Levarterenol Bitartrate Injection is the most suitable drug; *epinephrine should not be used* since phenothiazine derivatives have been found to reverse its action. Nausea, loss of appetite, salivation, polyuria, perspiration, dry mouth, headache, and constipation may occur. Reducing or temporarily discontinuing the dosage will usually control these effects. Blurred vision, glaucoma, bladder paralysis, fecal impaction, paralytic ileus, tachycardia, or nasal congestion have occurred in some patients on phenothiazine derivatives.

Metabolic and Endocrine: Weight change, peripheral edema, abnormal lactation, gynecomastia, menstrual irregularities, false results on pregnancy tests, impotency in men and increased libido in women have occurred in some patients on phenothiazine therapy.

Allergic Reactions: Itching, erythema, urticaria, seborrhea, photosensitivity, eczema and exfoliative dermatitis have been reported with phenothiazines. The possibility of anaphylactoid reactions should be borne in mind.

Hematologic: Blood dyscrasias including leukopenia, agranulocytosis, thrombocytopenic or nonthrombocytopenic purpura, eosinophilia, and pancytopenia have been observed with phenothiazines. If soreness of the mouth, gums or throat, or any symptoms of upper respiratory infection occur and confirmatory leukocyte count indicates cellular depression, therapy should be discontinued and other appropriate measures instituted immediately.

Hepatic: Liver damage manifested by cholestatic jaundice, particularly during the first months of therapy, may occur; treatment should be discontinued. A cephalin flocculation increase, sometimes accompanied by alterations in other liver function tests, has been reported in patients who have had no clinical evidence of liver damage.

Others: Sudden deaths have been reported in hospitalized patients on phenothiazines. Previous brain damage or seizures may be predisposing factors. High doses should be avoided in known seizure patients. Shortly before death, several patients showed flare-ups of psychotic behavior patterns. Autopsy findings have usually revealed acute fulminating pneumonia or pneumonitis, aspiration of gastric contents, or intramyocardial lesions. Although not a general feature of fluphenazine, potentiation of central nervous system depressants such as opiates, analgesics, antihistamines, barbiturates and alcohol may occur.

Systemic lupus erythematosus-like syndrome, hypotension severe enough to cause fatal cardiac arrest, altered electrocardiographic and electroencephalographic tracings, altered cerebrospinal fluid proteins, cerebral edema, asthma, laryngeal edema, and angioneurotic edema; with long-term use, skin pigmentation, and lenticular and corneal opacities have occurred with phenothiazines. Local tissue reactions occur only rarely with injections of fluphenazine decanoate.

HOW SUPPLIED: *Tablets*—1 mg, 2.5 mg, 5 mg, and 10 mg in bottles of 50, 100 and 500, and in Unimatic® cartons of 100. *Elixir*—in bottles of 473 mL (1 pint) and in 60 mL dropper-assembly bottles with calibrated dropper. *Oral Concentrate*—in bottles of 120 mL with calibrated dropper. *Injection*—in multiple-dose vials of 10 mL. *Fluphenazine Decanoate*—in 1 mL Unimatic® single dose preassembled syringes and 5 mL vials.

For full prescribing information, consult package inserts. (J4-120/147/153/150)

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The Chief, Clinical Pharmacology Research Branch, manages a staff of 15 and a budget of 4.2 million. Branch programs are carried out with volunteer subjects and test drugs for dependence potential, develop new pharmacological treatments, analyze the metabolic pathways of drugs, and devise drug detection systems for screening drugs in body fluid.

Educational requirements include graduation with a degree of Doctor of Medicine from an AMA approved medical school, or a Doctor of Osteopathy degree from an approved school. In addition, the applicant must possess a permanent and full license to practice medicine. Professional background and/or education must indicate an extensive knowledge of research methodology. Applicants must demonstrate progressively responsible experience in the scientific research administration and proven professional competence in areas related to the intramural research function. The experience must show evidence of involvement in research programs concerned with drug abuse related disorders and demonstrate a broad understanding of the biological, clinical, and behavioral sciences as they relate to the drug abuse field. Candidates must also have management experience demonstrating competence to assume leadership in planning, staffing, directing, and allocating resources for a major research program.

Submit applications (Application for Federal Employment, SF-171), accompanied by a current curriculum vitae and bibliography, to Ms. Lois Mercer, Division of Personnel Management, Alcohol, Drug Abuse, and Mental Health Administration, 5600 Fishers Lane, Room 15C26, Rockville, Maryland 20857 (Phone: 301/443-5030) Applications will be accepted without the SF-171, provided the SF-171 is submitted upon request. Nominations and applications should be submitted by May 29, 1987.

Applications from women and minority group members are especially solicited.

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Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, *1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to* Journal *readers will be included.*

JULY

July 19–24, First International Symposium on Management of Pain, Stress, Fear and Anxiety, Tel-Aviv, Israel. Contact Prof. Y. Sharav, Hebrew University-Hadassah, P.O. Box 1172, Jerusalem, 91010, Israel; 972-2-446146.

July 31–August 2, 8th Biennial MRI Conference, Solutions-Pseudosolutions-Ultrasolutions, San Francisco. Contact MRI Conference, 555 Middlefield Rd., Palo Alto, CA 94301; 415-321-3055.

AUGUST

August 2–6, annual conference, African Psychiatric Association, Harare, Zimbabwe. Contact Godfrey Huggins, School of Medicine, P.O. Box A 178, Avondale, Harare, Zimbabwe.

August 3–5, annual convention, American Hospital Association, Philadelphia. Contact H. Joseph Curl, Executive Vice-President, 840 North Lake Shore Dr., Chicago, IL 60611; 312-280-6000.

August 6–13, annual meeting, American Bar Association, San Francisco. Contact Thomas H. Gonser, Esq., Executive Director, 750 North Lake Shore Dr., Chicago, IL 60611; 312-988-5130.

August 9–13, annual meeting, American Institute of Biological Sciences, Columbus, Ohio. Contact Dr. Charles M. Chambers, Executive Director, 730 11th St., N.W., Washington, DC 20001-4584; 202-628-1500.

August 9–14, XIV Annual Symposium, Neuropsychiatric Aspects of Sociopathy, Kamuela, Hawaii. Contact Teresa Santana, S.C.N.P.I., 6794 La Jolla Blvd., La Jolla, CA 92037; 619-454-2102, 800-423-9521.

August 12–16, annual conference, American Association for Partial Hospitalization, Boston. Contact Joan Fridberg, 1221 Massachusetts Ave., N.W., Suite B, Washington, DC 20005; 202-347-1649.

August 17–21, annual meeting, American Sociological Association, Chicago. Contact Jen L. Suter, Meetings and Marketing Manager, ASA, 1722 N Street, N.W., Washington, DC 20036; 202-833-3410.

August 23–28, annual meeting, Canadian Medical Association, Charlottetown, Canada. Contact B.E. Freamo, Secretary-General, P.O. Box 8650, Ottawa, Ontario K1G 0G8, Canada; 613-731-9331.

August 28–September 1, annual meeting, American Psychological Association, New York. Contact Leonard D. Goodstein, Ph.D., Executive Officer, 1200 17th St., N.W., Washington, DC 20036; 202-955-7600.

August 30–September 1, annual meeting, International College of Psychosomatic Medicine, Sydney, Australia. Contact Professor Carins Aitken, M.D., Executive Director, Rehabilitation Studies Unit, Princess Margaret Rose Hospital, Edinburgh, EH10 7ED, Scotland.

SEPTEMBER

September 4–5, fall meeting, American Association for Social Psychiatry, New Orleans. Contact Carolyn B. Robinowitz, M.D., Secretary-Treasurer, AASP, 1400 K St., N.W., Washington, DC 20005; 202-682-6130.

September 9–12, annual meeting, National Association of Social Workers, New Orleans. Contact Mark G. Battle, A.C.S.W., Executive Director, 7981 Eastern Ave., Silver Spring, MD 20910; 301-565-0333.

September 9–13, 2nd International Symposium on Premenstrual, Postpartum and Menopausal Mood Disorders, Kiawah Island, S.C. Contact University of Medicine and Dentistry of New Jersey, Office of Continuing Education, 675 Hoes Ln., Piscataway, NJ 08854-5635; 201-463-4707.

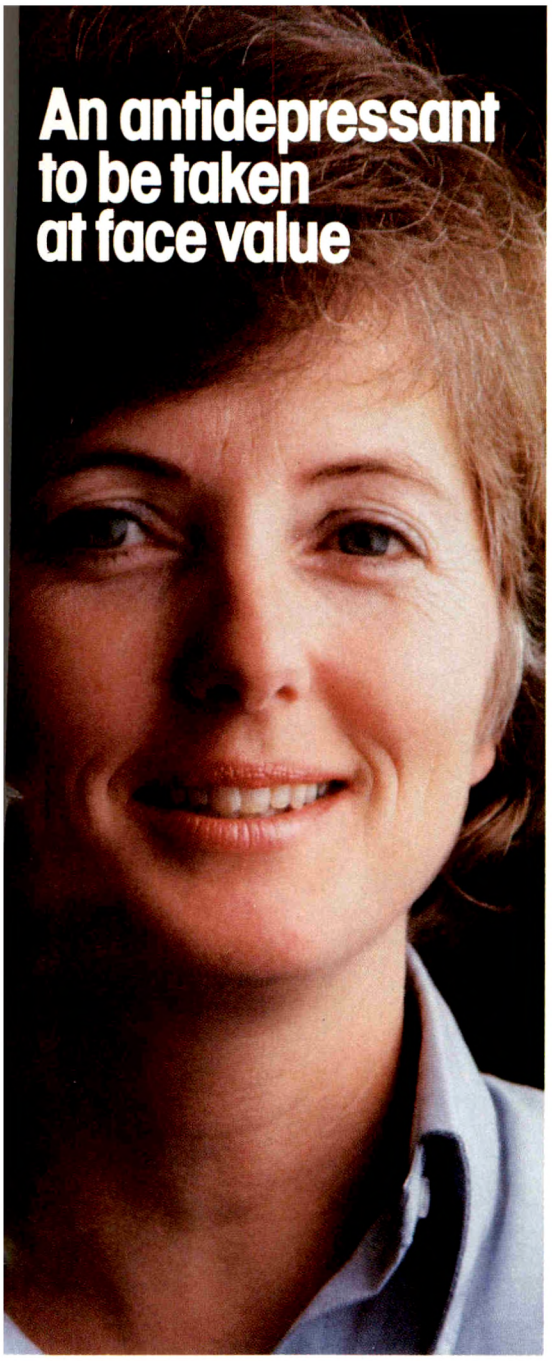
September 11–13, annual conference, Canadian Art Therapy Association, Vancouver, Canada. Contact CATA, Conference Committee, 216 St. Clair Avenue West, Toronto, Ontario M4V 1R2, Canada; 416-921-4374.

September 11–15, annual meeting, Royal College of Physicians and Surgeons of Canada, Winnipeg, Canada. Contact Dr. J.H. Darragh, Executive Director, 74 Stanley Ave., Ottawa, Ontario K1M 1P4, Canada; 613-746-8177.

September 13–15, annual meeting, Canadian Academy of Child Psychiatry, London, Ontario. Contact J.H. Beitchman, M.D., Program Chairman, CACP, Clarke Institute of Psychiatry, 250 College St., Toronto, Ontario M5T 1R8, Canada.

September 14–17, annual meeting, American Academy of Family Physicians, San Francisco. Contact Robert Graham,

(Continued on page A51)



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Because of anticholinergic activity, PAMELOR (nortriptyline HCl) should be used with caution in patients who have glaucoma or a history of urinary retention.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

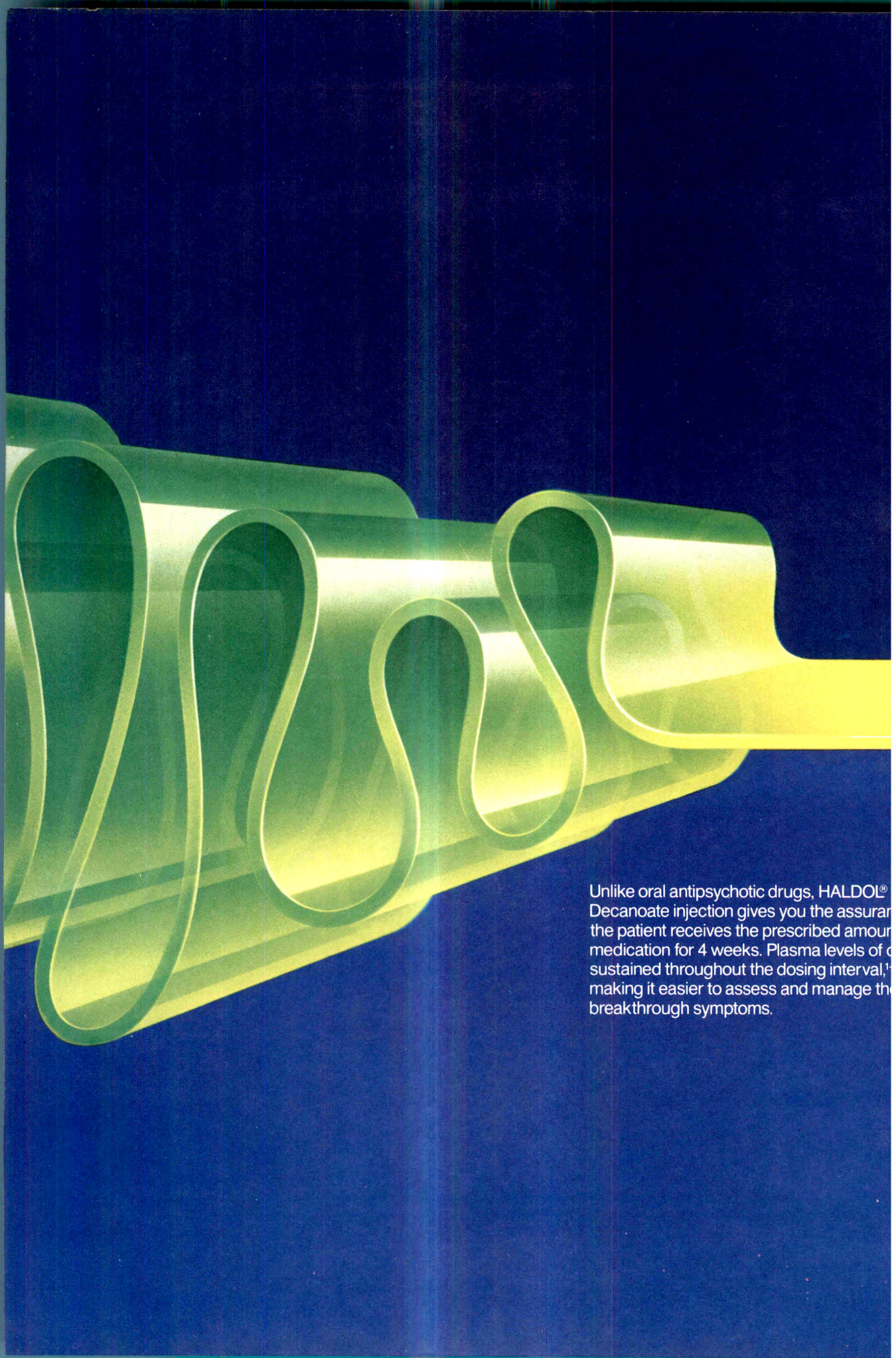
Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania, exacerbation of psychosis. *Neurologic*—Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. *Allergic*—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. *Hematologic*—Bone-marrow depression, including agranulocytosis; eosinophilia; purpura, thrombocytopenia. *Gastrointestinal*—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Other*—Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia. *Withdrawal Symptoms*—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage. [PAM-Z13—7-15-86]

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The side effects of HALDOL Decanoate are those of HALDOL. The prolonged action of HALDOL Decanoate should be considered in the management of side effects. During dose adjustment or episodes of exacerbation of psychotic symptoms, HALDOL Decanoate therapy can be supplemented with short-acting forms of HALDOL. It is recommended that patients being considered for HALDOL Decanoate therapy have, at some time, been treated with, and have tolerated well, short-acting HALDOL in order to exclude the possibility of unexpected adverse sensitivity to haloperidol. HALDOL Decanoate is administered only by deep intramuscular injection.

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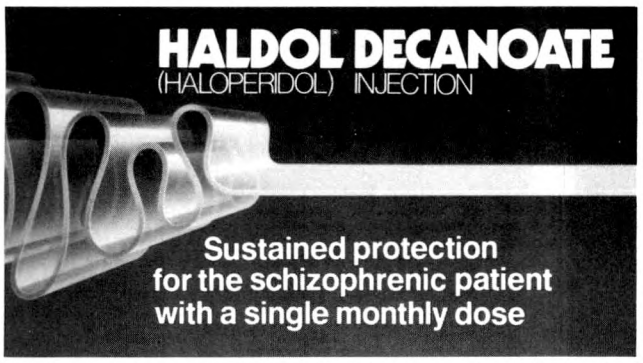
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Please see brief summary of prescribing information on next page.

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The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5 and 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis: the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions—Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia and tardive dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the full syndrome may not develop. *Other CNS Effects:* Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic Malignant Syndrome: As with other antipsychotic drugs, a symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported. Cardinal features of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. NMS is potentially fatal, requires intensive symptomatic treatment and immediate discontinuation of antipsychotic treatment. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported. *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed.

For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

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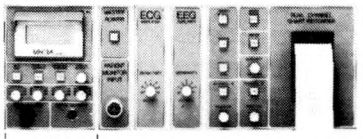
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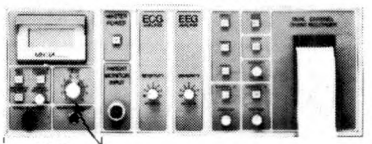


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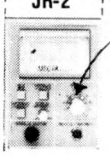
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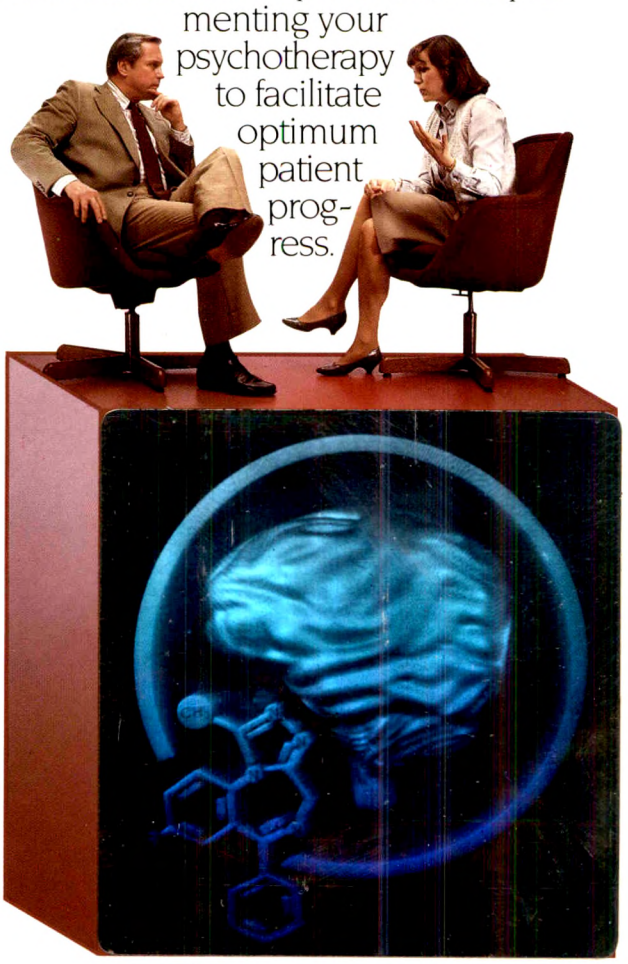
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CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or lightheadedness.

Central nervous system. Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

CAUTION: FEDERAL LAW PROHIBITS DISPENSING WITHOUT PRESCRIPTION.

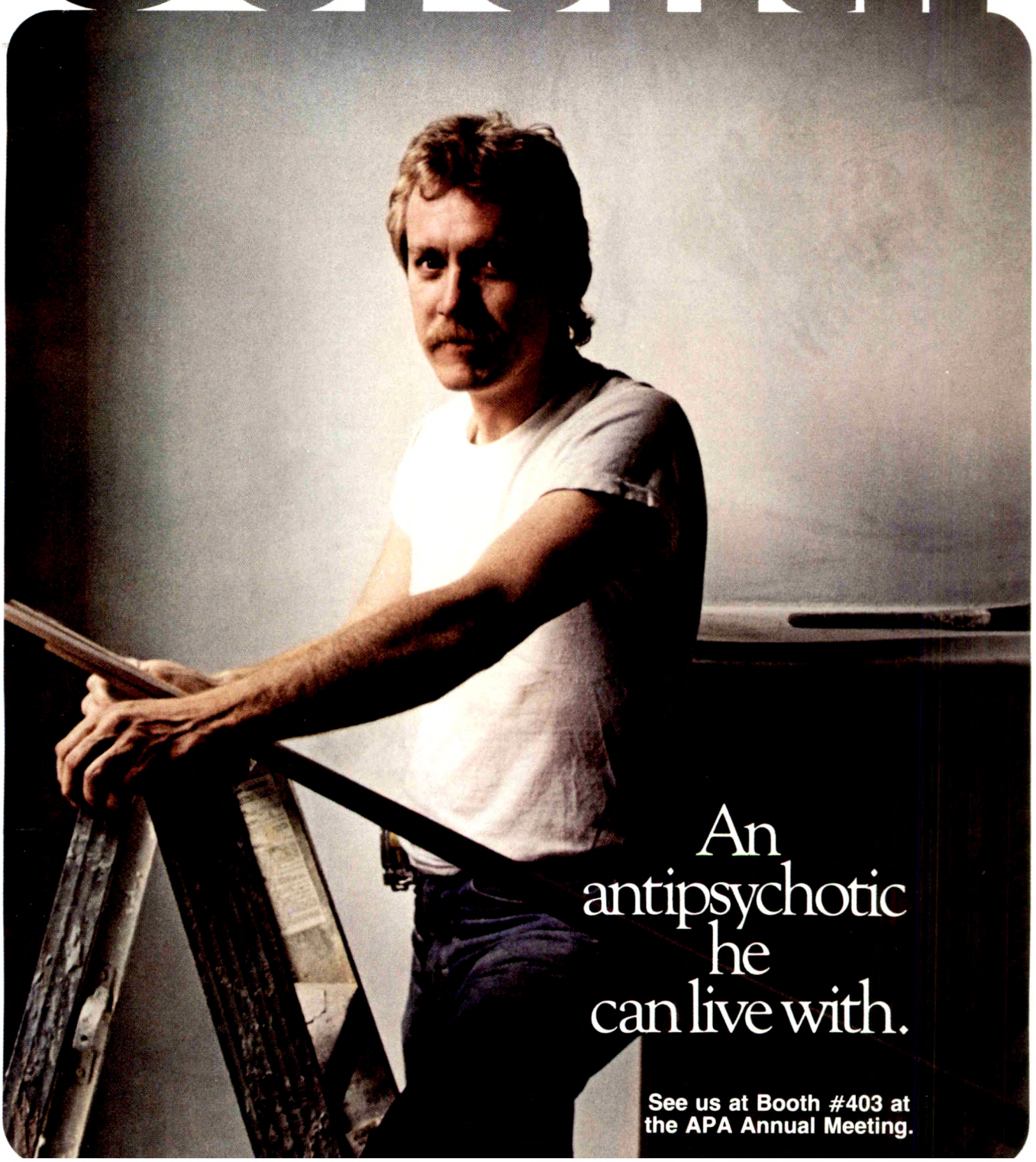
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Brief Summary of Prescribing Information

Contraindications: As with other phenothiazines, Serentil® (mesoridazine), is contraindicated in severe central nervous system depression or comatose states from any cause. Serentil is contraindicated in individuals who have previously shown hypersensitivity to the drug.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness 1) that is known to respond to neuroleptic drugs, and 2) for which alternative, equally effective but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for Patients and Adverse Reactions).

Where patients are participating in activities requiring complete mental alertness (e.g. driving) it is advisable to administer the phenothiazines cautiously and to increase the dosage gradually.

Usage in Pregnancy: The safety of this drug in pregnancy has not been established; hence, it should be given only when the anticipated benefits to be derived from treatment exceed the possible risks to mother and fetus.

Usage in Children: The use of Serentil (mesoridazine) in children under 12 years of age is not recommended, because safe conditions for its use have not been established.

Attention should be paid to the fact that phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides.

Precautions: While ocular changes have not to date been related to Serentil® (mesoridazine), one should be aware that such changes have been seen with other drugs of this class.

Because of possible hypotensive effects, reserve parenteral administration for bedfast patients or for acute ambulatory cases, and keep patient lying down for at least one-half hour after injection.

Leukopenia and/or agranulocytosis have been attributed to phenothiazine therapy. A single case of transient granulocytopenia has been associated with Serentil. Since convulsive seizures have been reported, patients receiving anticonvulsant medication should be maintained on that regimen while receiving Serentil.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Information for Patients: Given the likelihood that some patients exposed chronically to neuroleptics will develop tardive dyskinesia, it is advised that all patients in whom chronic use is contemplated be given, if possible, full information about this risk.

Adverse Reactions: Drowsiness and hypotension were the most prevalent side effects encountered. Side effects tended to reach their maximum level of severity early with the exception of a few (rigidity and motoric effects) which occurred later in therapy.

With the exceptions of tremor and rigidity, adverse reactions were generally found among those patients who received relatively high doses early in treatment. Clinical data showed no tendency for the investigators to terminate treatment because of side effects.

Serentil® (mesoridazine) has demonstrated a remarkably low incidence of adverse reactions when compared with other phenothiazine compounds.

Central Nervous System: Drowsiness, Parkinson's syndrome, dizziness, weakness, tremor, restlessness, ataxia, dystonia, rigidity, slurring, akathisia, motoric reactions (opisthotonos) have been reported.

Autonomic Nervous System: Dry mouth, nausea and vomiting, fainting, stuffy nose, photophobia, constipation and blurred vision have occurred in some instances.

Genitourinary System: Inhibition of ejaculation, impotence, enuresis, incontinence have been reported.

Skin: Itching, rash, hypertrophic papillae of the tongue and angioneurotic edema have been reported.

Cardiovascular System: Hypotension and tachycardia have been reported. EKG changes have occurred in some instances (see Phenothiazine Derivatives: Cardiovascular Effects).

Phenothiazine Derivatives: It should be noted that efficacy, indications and untoward effects have varied with the different phenothiazines. The physician should be aware that the following have occurred with one or more phenothiazines and should be considered whenever one of these drugs is used:

Autonomic Reactions: Miosis, obstipation, anorexia, paralytic ileus.

Cutaneous Reactions: Erythema, exfoliative dermatitis, contact dermatitis.

Blood Dyscrasias: Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia.

Allergic Reactions: Fever, laryngeal edema, angioneurotic edema, asthma.

Hepatotoxicity: Jaundice, biliary stasis.

Cardiovascular Effects: Changes in the terminal portion of the electrocardiogram, including prolongation of the Q-T interval, lowering and inversion of the T wave and appearance of a wave tentatively identified as a bifid T or a U wave have been observed in some patients receiving the phenothiazine tranquilizers, including Serentil® (mesoridazine). To date, these appear to be due to altered repolarization and not related to myocardial damage. They appear to be reversible. While there is no evidence at present that these changes are in any way precursors of any significant disturbance of cardiac rhythm, it should be noted that sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients previously showing characteristic electrocardiographic changes while taking the drug. The use of periodic electrocardiograms has been proposed but would appear to be of questionable value as a predictive device. Hypotension, rarely resulting in cardiac arrest, has been noted.

Extrapyramidal Symptoms: Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonos, oculogyric crises, tremor, muscular rigidity, akinesia.

Tardive Dyskinesia: Chronic use of neuroleptics may be associated with the development of tardive dyskinesia. The salient features of this syndrome are described in the **Warnings** section and below.

The syndrome is characterized by involuntary choreoathetoid movements which variously involve the tongue, face, mouth, lips, or jaw (e.g. protrusion of the tongue, puffing of cheeks, puckering of the mouth, chewing movements), trunk and extremities. The severity of the syndrome and the degree of impairment produced vary widely.

The syndrome may become clinically recognizable either during treatment, upon dosage reduction, or upon withdrawal of treatment. Movements may decrease in intensity and may disappear altogether if further treatment with neuroleptics is withheld. It is generally believed that reversibility is more likely after short rather than long-term neuroleptic exposure. Consequently, early detection of tardive dyskinesia is important. To increase the likelihood of detecting the syndrome at the earliest possible time, the dosage of neuroleptic drug should be reduced periodically (if clinically possible) and the patient observed for signs of the disorder. This maneuver is critical, for neuroleptic drugs may mask the signs of the syndrome.

Endocrine Disturbances: Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema. False positive pregnancy tests have been reported.

Urinary Disturbances: Retention, incontinence.

Others: Hyperpyrexia. Behavioral effects suggestive of a paradoxical reaction have been reported. These include excitement, bizarre dreams, aggravation of psychoses and toxic confusional states. More recently, a peculiar skin-eye syndrome has been recognized as a side effect following long-term treatment with phenothiazines. This reaction is marked by progressive pigmentation of areas of the skin or conjunctiva and/or accompanied by discoloration of the exposed sclera and cornea. Opacities of the anterior lens and cornea described as irregular or stellate in shape have also been reported. Systemic lupus erythematosus-like syndrome.

How Supplied:

Serentil® Tablets, for oral administration: 10 mg, 25 mg, 50 mg, and 100 mg mesoridazine (as the besylate). Bottles of 100.

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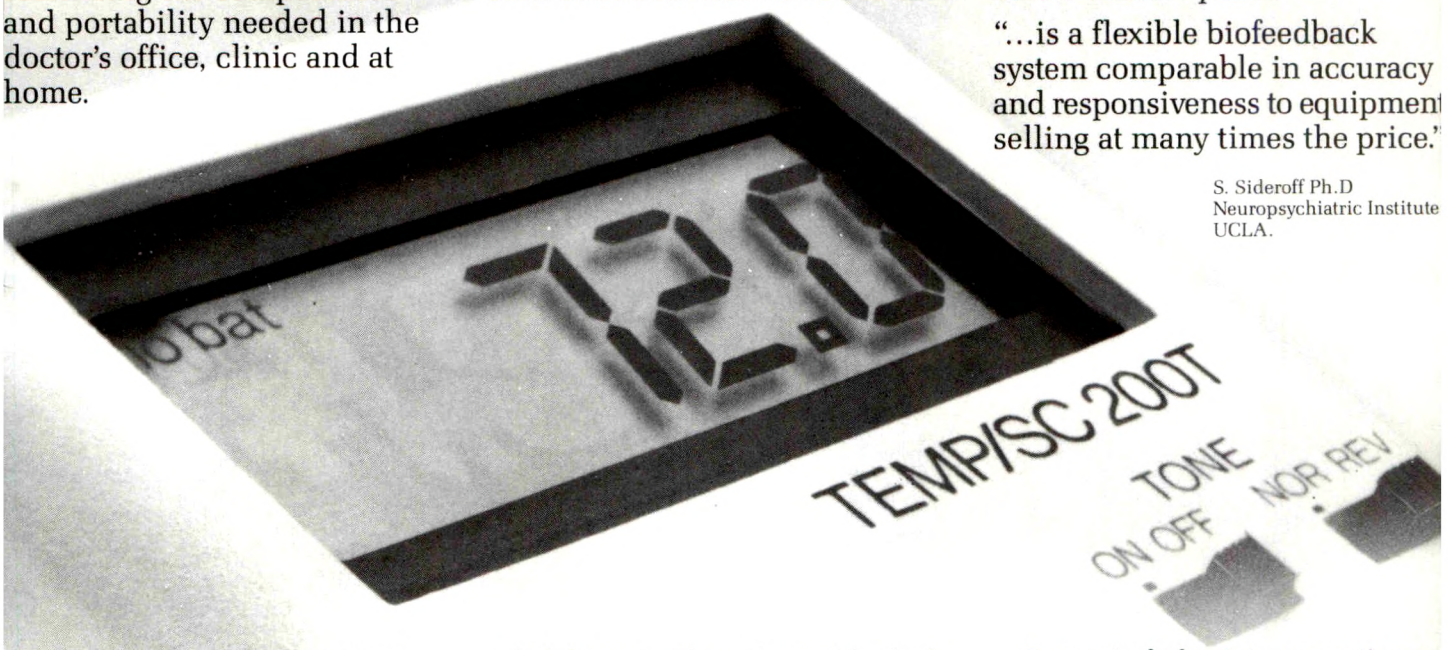
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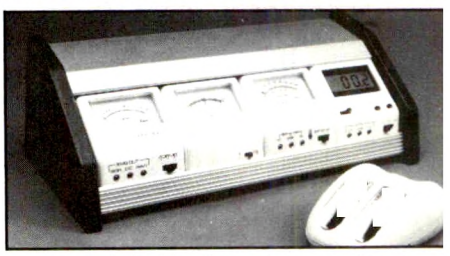
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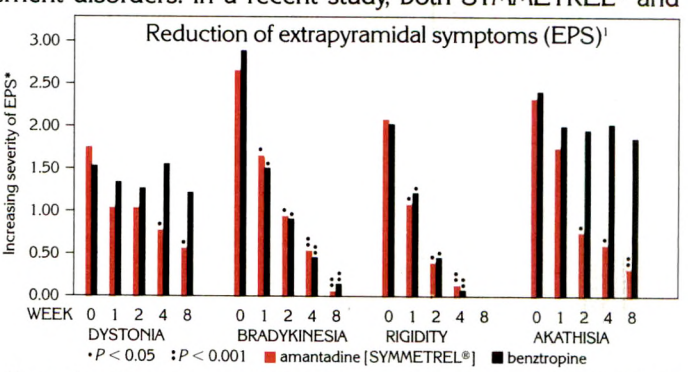


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*Extrapyramidal symptoms were rated on a four-point scale of ascending severity. —adapted from Borison and Diamond, p 42[1]

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Incidence of anticholinergic side effects[1]

	% patients taking amantadine	% patients taking benztropine
Dry mouth	7.4	41.6
Blurred vision	2.6	26.5
Nasal congestion	2.5	18.2
Constipation	1.8	21.4
Urinary hesitancy	1.3	7.1

—adapted from Borison and Diamond, p 43[1]

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Please see following page for brief summary of prescribing information.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE: *Parkinson's Disease/Syndrome and Drug-Induced Extrapyramidal Reactions:* SYMMETREL is indicated in the treatment of idiopathic Parkinson's disease (Paralysis Agitans), postencephalitic parkinsonism, drug-induced extrapyramidal reactions, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication. It is indicated in those elderly patients believed to develop parkinsonism in association with cerebral arteriosclerosis. In the treatment of Parkinson's disease, SYMMETREL is less effective than levodopa, (-)-3-(3, 4-dihydroxyphenyl)-L-alanine, and its efficacy in comparison with the anticholinergic antiparkinson drugs has not yet been established. Although anticholinergic type side effects have been noted with SYMMETREL when used in patients with drug-induced extrapyramidal reactions, there is a lower incidence of these side effects than that observed with anticholinergic antiparkinson drugs.

CONTRAINDICATIONS: SYMMETREL is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Patients with a history of epilepsy or other "seizures" should be observed closely for possible increased seizure activity.

Patients with a history of congestive heart failure or peripheral edema should be followed closely as there are patients who developed congestive heart failure while receiving SYMMETREL.

Patients with Parkinson's disease improving on SYMMETREL should resume normal activities gradually and cautiously, consistent with other medical considerations, such as the presence of osteoporosis or phlebothrombosis.

Patients receiving SYMMETREL who note central nervous system effects or blurring of vision should be cautioned against driving or working in situations where alertness is important.

PRECAUTIONS: SYMMETREL (amantadine hydrochloride) should not be discontinued abruptly since a few patients with Parkinson's disease experienced a parkinsonian crisis, i.e., a sudden marked clinical deterioration, when this medication was suddenly stopped. The dose of anticholinergic drugs or of SYMMETREL should be reduced if atropine-like effects appear when these drugs are used concurrently.

The dose of SYMMETREL may need careful adjustment in patients with renal impairment, congestive heart failure, peripheral edema, or orthostatic hypotension. Since SYMMETREL is not metabolized and is mainly excreted in the urine, it may accumulate when renal function is inadequate.

Care should be exercised when administering SYMMETREL to patients with liver disease, a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents. Careful observation is required when SYMMETREL is administered concurrently with central nervous system stimulants.

No long-term studies in animals have been performed to evaluate the carcinogenic potential of SYMMETREL. The mutagenic potential of the drug has not yet been determined in experimental systems.

Pregnancy Category C: SYMMETREL (amantadine hydrochloride) has been shown to be embryotoxic and teratogenic in rats at 50 mg/kg/day, about 12 times the recommended human dose, but not at 37 mg/kg/day. Embryotoxic and teratogenic drug effects were not seen in rabbits which received up to 25 times the recommended human dose. There are no adequate and well-controlled studies in pregnant women.

SYMMETREL should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or the fetus.

Nursing Mothers: SYMMETREL is excreted in human milk. Caution should be exercised when SYMMETREL is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SYMMETREL in newborn infants, and infants below the age of 1 year have not been established.

ADVERSE REACTIONS: The most frequently occurring serious adverse reactions are depression, congestive heart failure, orthostatic hypotensive episodes, psychosis, and urinary retention. Rarely convulsions, leukopenia, and neutropenia have been reported.

Other adverse reactions of a less serious nature which have been observed are the following: hallucinations, confusion, anxiety; irritability; anorexia, nausea, and constipation; ataxia and dizziness (lightheadedness); livedo reticularis and peripheral edema. Adverse reactions observed less frequently are the following: vomiting; dry mouth; headache; dyspnea; fatigue, insomnia, and a sense of weakness. Infrequently, skin rash, slurred speech, and visual disturbances have been observed. Rarely eczematoid dermatitis and oculogyric episodes have been reported.

DOSAGE AND ADMINISTRATION: Adult Dosage for Parkinsonism: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day when used alone. SYMMETREL has an onset of action usually within 48 hours.

The initial dose of SYMMETREL is 100 mg daily for patients with serious associated medical illnesses or who are receiving high doses of other antiparkinson drugs. After one to several weeks at 100 mg once daily, the dose may be increased to 100 mg twice daily, if necessary.

Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 400 mg daily in divided doses. However, such patients should be supervised closely by their physicians.

Patients initially deriving benefit from SYMMETREL not uncommonly experience a fall-off of effectiveness after a few months. Benefit may be regained by increasing the dose to 300 mg daily. Alternatively, temporary discontinuation of SYMMETREL for several weeks, followed by reinitiation of the drug, may result in regaining benefit in some patients. A decision to use other antiparkinson drugs may be necessary.

Dosage for Concomitant Therapy: Some patients who do not respond to anticholinergic antiparkinson drugs may respond to SYMMETREL. When SYMMETREL or anticholinergic antiparkinson drugs are each used with marginal benefit, concomitant use may produce additional benefit.

When SYMMETREL and levodopa are initiated concurrently, the patient can exhibit rapid therapeutic benefits. SYMMETREL should be held constant at 100 mg daily or twice daily while the daily dose of levodopa is gradually increased to optimal benefit.

When SYMMETREL is added to optimal well-tolerated doses of levodopa, additional benefit may result, including smoothing out the fluctuations in improvement which sometimes occur in patients on levodopa alone. Patients who require a reduction in their usual dose of levodopa because of the development of side effects may possibly regain lost benefit with the addition of SYMMETREL.

Dosage for Drug-Induced Extrapyramidal Reactions: Adult: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day. Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 300 mg daily in divided doses. 6043-15BSP/Rev. Oct. 1984

Capsules manufactured by R. P. Scherer-North America, St. Petersburg, Florida 33702 for

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REFERENCE: 1. Borison RL, Diamond BI: Treatment of extrapyramidal side-effects: Amantadine versus benztropine. *World J Psychosynthesis* (special), 1984-1985, pp 40-43.

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Contraindications: Severe central nervous system depression, comatose states from any cause, hypertensive or hypotensive heart disease of extreme degree.

Warnings: The risk of developing potentially irreversible *tardive dyskinesia* is believed to increase as duration of treatment and total cumulative dose increase, although it is impossible to predict who will develop the syndrome. It can also develop, although much less commonly, after brief treatment with low doses. Incidence appears to be highest among the elderly, especially elderly women. Generally chronic treatment should be reserved for chronically ill patients whose disease is most likely to respond to neuroleptic drugs and for whom other effective, less harmful treatment is not available or appropriate. There is no known treatment for tardive dyskinesia although the syndrome may partially or completely remit upon withdrawal of neuroleptic treatment. If signs and symptoms of tardive dyskinesia appear, drug discontinuation should be considered. Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides; carefully consider benefit versus risk in less severe disorders. During pregnancy, administer only when the potential benefits exceed the possible risks to mother and fetus.

Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy, observed primarily in patients receiving larger than recommended doses, is characterized by diminution of visual acuity, brownish coloring of vision, and impairment of night vision; the possibility of its occurrence may be reduced by remaining within recommended dosage limits. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving), and increase dosage gradually. Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension since phenothiazines may induce a reversed epinephrine effect on occasion.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. Daily doses in excess of 300 mg should be used only in severe neuropsychiatric conditions.

Information for Patients: It is suggested that all patients who are candidates for chronic treatment be advised of the risk of tardive dyskinesia.

Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; rarely, nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—ECG changes (see *Cardiovascular Effects* below). *Other*—Rare cases described as parotid swelling.

It should be noted that efficacy, indications and untoward effects have varied with the different phenothiazines. It has been reported that old age lowers the tolerance for phenothiazines; the most common neurological side effects are parkinsonism and akathisia, and the risk of agranulocytosis and leukopenia increases. The following reactions have occurred with phenothiazines and should be considered whenever one of these drugs is used:

Autonomic Reactions—Miosis, obstipation, anorexia, paralytic ileus. *Cutaneous Reactions*—Erythema, exfoliative dermatitis, contact dermatitis. *Blood Dyscrasias*—Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia. *Allergic Reactions*—Fever, laryngeal edema, angioneurotic edema, asthma. *Hepatotoxicity*—Jaundice, biliary stasis. *Cardiovascular Effects*—Changes in the terminal portion of electrocardiogram including prolongation of Q-T interval, lowering and inversion of T-wave, and appearance of a wave tentatively identified as a bifid T or a U wave have been observed with phenothiazines, including Mellaril (thioridazine); these appear to be reversible and due to altered repolarization, not myocardial damage. While there is no evidence of a causal relationship between these changes and significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients showing characteristic electrocardiographic changes while taking the drug. While proposed, periodic electrocardiograms are not regarded as predictive. Hypotension, rarely resulting in cardiac arrest. *Extrapyramidal Symptoms*—Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonus, oculogyric crises, tremor, muscular rigidity, and akinesia. *Tardive Dyskinesia*—Characterized by involuntary choreoathetoid movements variously involving the tongue, face, mouth, lips or jaw (e.g., protrusion of the tongue, puffing of the cheeks, puckering of the mouth, chewing movements), trunk and extremities—may be recognized during treatment upon dosage reduction or withdrawal of treatment. Movements may decrease or disappear if further treatment is withheld, although this reversibility is more likely after short-term rather than long-term treatment. Since neuroleptics may mask the signs of tardive dyskinesia, reducing dosage periodically increases the likelihood of detecting the syndrome at the earliest possible time. *Endocrine Disturbances*—Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema, false positive pregnancy tests. *Urinary Disturbances*—Retention, incontinence. *Others*—Hyperpyrexia; behavioral effects suggestive of a paradoxical reaction, including excitement, bizarre dreams, aggravation of psychoses, and toxic confusional states; following long-term treatment, a peculiar skin-eye syndrome marked by progressive pigmentation of skin or conjunctiva and/or accompanied by discoloration of exposed sclera and cornea; stellate or irregular opacities of anterior lens and cornea; systemic lupus erythematosus-like syndrome.

Dosage: Dosage must be individualized according to the degree of mental and emotional disturbance, and the smallest effective dosage should be determined for each patient. [MEL-Z37—5/1/85]

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THE AMERICAN JOURNAL OF PSYCHIATRY

The Psychodynamic Formulation: Its Purpose, Structure, and Clinical Application

Samuel Perry, M.D., Arnold M. Cooper, M.D., and Robert Michels, M.D.

The authors present a brief written psychodynamic formulation that focuses on central conflicts, anticipates transferences and resistances, and helps guide all psychiatric treatments. After placing the presenting problem in the context of the patient's life and identifying nondynamic determinants of the psychopathology, the formulation explains the development of central conflicts and their repetitive effect on the patient's behavior. It concludes by describing how these conflicts will be manifested in treatment. Three sample formulations and their application are presented to illustrate the value of this clinical tool.

(Am J Psychiatry 1987; 144:543–550)

In the course of supervising mental health professionals, we have noted that a comprehensive psychodynamic formulation is seldom offered and almost never incorporated into the written record. Our experience is reflected in the psychiatric and psychoanalytic literature, where psychodynamics are often discussed but psychodynamic formulations are rarely presented. In this paper we discuss the purpose and structure of the psychodynamic formulation, provide three illustrations, and indicate how these formulations can help guide all treatments.

PURPOSE OF THE FORMULATION

In many respects a dynamic formulation and a clinical diagnosis share a common purpose. Although both hold intellectual, didactic, and research interests, their primary function is to provide a succinct conceptualization of the case and thereby guide a treatment plan. Like a psychiatric diagnosis, a psychodynamic formulation is specific, brief, focused, and therefore limited in its intent, scope, and wisdom. It concisely and incisively clarifies the central issues and conflicts, differentiating what the therapist sees as essential from what is secondary. Also like the diagnosis, additional information and changes over time may lead to modifications of the patient's dynamics and how they are formulated, with corresponding alterations in treatment. Again, like the diagnosis, the psychodynamic understanding of a patient serves as a stabilizing force in conducting any form of therapy; its general effect is conservative, discouraging a change in tack with every slight shift of the wind.

One common misconception is that a psychodynamic formulation is indicated only for those patients in a long-term, expressive psychotherapy. This belief ignores the fact that the success of any treatment may involve supporting, managing, or even modifying aspects of the patient's personality. Therapeutic effectiveness or failure often hinges on how well or poorly the therapist understands the patient's dynamics, predicts what resistances the patient will present, and designs an approach that will circumvent, undermine, or surmount these obstacles.

A second common misconception is that the construction of a psychodynamic formulation is primarily a training experience. For example, MacKinnon and Yudofsky (1), while agreeing with the importance of understanding a patient's psychodynamics, state: "A written case formulation is principally for the education of the clinician or for clinical case conferences. The thought and preparation involved in this exercise constitute an important learning experience for the beginning student of psychiatry." These authors then later suggest, "Even an experienced therapist can benefit from this task in a confusing or difficult case."

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Although MacKinnon and Yudofsky are here referring to a complete case formulation (which includes the present illness, psychopathology, developmental data, diagnostic classification, and prognosis), one may erroneously conclude that a written psychodynamic formulation is a task reserved for special situations rather than a fundamental component of all treatments.

A third common misconception, related to the second, is that the construction of a psychodynamic formulation must be elaborate and time-consuming. This view derives in part from various reviews in the psychiatric literature that, in an attempt to be inclusive, describe in detail all the requirements of a thorough evaluation (1–4) or the multiple dynamic conflicts that may influence any aspect of human behavior (5, 6). The trainee may get the impression that anything short of an exhaustive dynamic explanation of each symptom or character trait is too simplified to be of value. This impression is often inadvertently reinforced when the supervisor points out some less essential aspects of the case that have been omitted in the condensed overview. A more helpful didactic approach accepts that the initial formulation is by necessity partial and tentative, but by describing the patient's leading unconscious needs and incipient defenses, the formulation may be sufficient to predict initial transferences and guide supportive or directive interventions. In time, as the clinical impression deepens, the linkage of current behavior to formative experiences and intrapsychic conflicts will become more clear and substantiated.

A fourth misconception is the notion that the formulation need not be written, as though somehow a patient's psychodynamics "go without saying." Our concern here is that if the formulation is never actually constructed and recorded, the patient's psychodynamics will remain mysterious, ambiguous, and all encompassing. E.M. Forster allegedly said, "I never know what I think until I read what I write." His point—and ours—is that the process of writing helps one achieve a clearer point of view. The written psychodynamic formulation is therefore valuable, even if seen only by the therapist who wrote it. The therapist who has a clear formulation of the patient's central conflicts is more capable of communicating that understanding to the patient in a consistent way. In addition, the dynamically prepared therapist is more likely to anticipate and recognize patterns of resistance or acting out than lag one step behind, using ad hoc (or even post hoc) formulations to respond to specific events.

A fifth and final misconception is that therapists will become so invested in their dynamic formulations that they will not be able to hear or accept material that does not fit a preconceived mold. On the contrary, constructing a dynamic formulation helps one to recognize its incompleteness, to inquire about pieces of the puzzle that are missing, to appreciate that not every piece fits neatly into place, and to accept the inevitable complexities and limited knowledge of every clinical situation. Furthermore, the formulation not only helps therapists accept their own limitations, it helps them accept the patient's pathology as well. The patient's behaviors in treatment—dependent, angry, avoidant, defiant, passive-aggressive, seductive, suspicious, noncompliant, and so on—are seen as manifestations of the patient's dynamics, as characteristic problems that can be predicted and understood and for which therapeutic interventions have been planned. As a result, the patient is not put in the paradoxical and untenable position of having to overcome his or her psychopathology as a prerequisite for treatment.

STRUCTURE OF THE FORMULATION

As we conceive it, the psychodynamic formulation is relatively brief (500–750 words) and has four parts: 1) a summary of the case that describes the patient's current problems and places them in the context of the patient's current life situation and developmental history; 2) a description of nondynamic factors that may have contributed to the psychiatric disorder; 3) a psychodynamic explanation of the central conflicts, describing their role in the current situation and their genetic origins in the developmental history; and 4) a prediction of how these conflicts are likely to affect treatment and the therapeutic relationship.

Part 1: Summarizing Statement

The opening paragraph outlines why this particular patient presents with this diagnosis and these particular problems at this particular time. By eliminating extraneous information, it succinctly identifies the patient, the precipitating events, the extent and quality of interpersonal relationships, the most salient predisposing features of the past history, and those prominent behaviors which the formulation will attempt to explain psychodynamically. This outline is not intended to summarize the entire case but rather to highlight the clinical situation that the psychodynamic formulation will address. By analogy, these first sentences are similar to the condensed admission note placed in the medical chart by the ward attending physician in contrast to the detailed history presented by the third-year medical student.

Part 2: Description of Nondynamic Factors

After the essential features of the case have been thoughtfully distilled, this second paragraph mentions the nondynamic factors that may have contributed to the psychiatric disorder, such as genetic predisposition, mental retardation, social deprivation, overwhelming trauma, and drugs or any physical illness affecting the brain. Noting other etiological factors sidesteps two potential pitfalls. First, it underscores that even if nondynamic factors have played a major role in causing the disorder, the psychodynamics of the patient cannot be ignored in the choice and implementation of

the treatment (2). Second, mentioning other etiological factors serves as a reminder that certain experiences of the patient may have psychodynamic meaning even though they do not stem from psychodynamic causes. Because meaning and cause are often confused, the clinical value of distinguishing the two is worth illustrating with the following brief vignettes.

Example 1. A homemaker with a very strong personal and family history of bipolar affective illness develops another major depressive episode when her youngest child leaves for college. It would be an error to ignore the likely contribution of genetic factors in the etiology of her depression, to attribute it solely to conflicts precipitated by the child's departure, and to fail to consider pharmacological interventions. However, even though the biological predisposition is essential for the occurrence of the illness, both the biology and the precipitating trigger must be understood psychosocially with their dynamic meanings. The feelings of unworthiness and guilt accompanying the depression may, for example, represent an unforgivable gap between a need to be a perfect mother and a self-image (conscious or unconscious) of being imperfect, bitter, angry, and uncaring. The therapist who understands these specific dynamics may therefore state, "Your youngest child's leaving and this depression make you feel that you have failed as a mother, a role that is very important to you." Such dynamically informed empathic remarks may tighten the therapeutic alliance, be therapeutic in their effect, increase compliance with medication if that is indicated, and synergistically enhance a placebo response.

Example 2. A young man with paranoid schizophrenia becomes disorganized under the stress of writing his senior college thesis. He becomes convinced that his previously admired political science professor is now using a KGB device to control the patient's thoughts and prevent the unusually perceptive manuscript from being published. While recognizing the biological and environmental factors that have caused the psychotic episode, the dynamic formulation also helps explain the meaning of the delusion: the conscious wish for acclaim and the fear of being controlled; the preconscious recognition of being inadequate and of losing control; and the unconscious wish to be controlled, an intolerable wish that is associated with vulnerable dependency and therefore projected. Equipped with this dynamic understanding, the therapist can tailor his or her interventions accordingly. For example, in the neuroleptic management, the therapist will consider the patient's fears of being controlled by explaining in detail the type, dosage, rationale, risks, benefits, and side effects of all medication. The therapeutic stance will be influenced by the meaning of the patient's relationship with the college professor; the therapist will avoid a premature frightening intimacy as he or she remains a somewhat distant but friendly helper who is especially candid and honest yet does not expect or require the patient's trust or submission. The psychotherapeutic interventions will address the conscious wishes and fears (e.g., "You wanted to write an outstanding thesis but felt the professor was controlling you") and in time the preconscious concern (e.g., "You were worried you weren't doing well"), but because pointing out unconscious wishes (e.g., "You secretly would like to be cared for") would be perceived as intrusive and similar to the professor's thought control, these interpretations would be avoided. The point here is not to describe the treatment of paranoid psychosis but to illustrate how an appreciation of a specific patient's psychodynamics can be useful in guiding the clinical management even in the presence of situational and biological determinants of the disorder.

Example 3. A woman is biologically predisposed to panic attacks that respond to imipramine maintenance; however, the psychodynamic formulation reveals that for this rigid Catholic patient the attacks represent both fears of and wishes for losing control, a state that is unconsciously perceived as an opportunity for the expansion of forbidden sexual wishes. In response to the fear, the patient at times overmedicates herself with the tricyclic or becomes agoraphobic; in response to the wish, she sometimes "forgets" her medication, has a panic attack, and then becomes disproportionately guilty and depressed for being "irresponsible" (and for unconsciously acting on forbidden impulses). Accordingly, in consideration of the psychodynamic meaning associated with this patient's biological disorder, the therapist combines his or her pharmacological management with directive, exploratory, and expressive techniques, advising the patient to read appropriate materials that explain the nature of the disorder and diminish unwarranted concerns of acting irresponsibly during an attack, exploring and clarifying for the patient the developmental derivatives of her conflict, and encouraging the patient to recount her dreams and fantasies. This dynamically informed process enables the patient to understand her illness and its meaning, to express her sexual wishes more adaptively than by her intermittent noncompliance with medication, and over time to feel less guilty about her forbidden desires.

Example 4. A fireman hospitalized for a severe burn develops a posttraumatic stress disorder. The psychodynamic formulation acknowledges the situational precipitants but also elucidates that for this man the intrusive thoughts and nightmares represent a conscious fear of going crazy and an unconscious fear of being a helpless dependent boy, a fear he has reacted against over the years by assuming a machismo style. In consideration of these dynamics, the psychiatric consultant addresses not only the conscious fear by reassuringly educating the patient about his acute posttraumatic stress disorder and its favorable prognosis, but also addresses the unconscious fear of passivity by supporting the patient's manliness and the heroic nature of his injury. This permits the development of a transference relationship in which the terror of the trauma can be reworked.

Example 5. An elderly retired executive with a mild dementia has become so rigid and demanding that his wife has lost her freedom and patience. The psychodynamic formulation accepts the organic determinants of his change in behavior, but also notes that the patient's inflexibility is partly due to a long-standing conscious need to be in charge, a recent preconscious recognition of his cognitive decline, unconscious feelings of anxiety and shame related to loss of adult capacities, and reparative attempts to maintain a sense of security and control by regulating his own life and the lives of those around him. By explaining these dynamics to the wife the therapist increases her tolerance, and by suggesting more adaptive ways for the patient to feel secure (clocks in every room, limited demands and expectations, consistent environment, titrated stimuli, written schedule, and so forth) the therapist is able to channel his or her dynamic understanding into simple, practical interventions.

These highly condensed examples are not intended to illustrate all the subtleties, complexities, and applications of a psychodynamic formulation but merely to indicate that the presence of nondynamic factors—genetic, traumatic, organic, and so forth—does not preclude the clinical value of understanding a patient's psychodynamics and, conversely, that a psychodynamic formulation does not ignore the effect of nondynamic factors on the patient's mood, thoughts, and behavior. The dynamic formulation is consistent with the biopsychosocial model (7), is relevant to all forms of psychiatric treatment, and is not reserved only for those psychiatric conditions in which biological features are less well defined (e.g., personality disorders) and only for those treatments that are insight oriented (e.g., exploratory psychotherapy). Even for disorders that are more clearly nondynamic in their etiology (e.g., schizophrenia, dementia) and for treatments that are more biomedical in their approach (e.g., psychopharmacotherapy), the therapist who formulates not only the cause but also the specific meaning of the illness will be better prepared, when appropriate, to communicate this understanding empathically (8) and to intervene effectively rather than with stereotyped responses. A "pseudohumanitarian" approach, a form of verbal handholding that does not consider the character style of a particular patient, may be experienced by paranoid patients as intrusive, by histrionic patients as seductive, by obsessive patients as demeaning, by depressed patients as undeserved and therefore guilt provoking, and by dependent or phobic patients as a sanction for further regression or avoidance. To be effective, the therapist must recognize those capacities of the patient which are temporarily or permanently deficient and for which "an auxiliary ego" is indicated, the unconscious meanings of these defects to the patient, and the available strengths of the patient that will be encouraged and enhanced. As described later the psychodynamic formulation facilitates this task by helping the therapist to conceptualize the issues systematically rather than relying only on intuition.

Part 3: Psychodynamic Explanation of Central Conflicts

If the first part of a psychodynamic formulation is similar to a clarification (a synthetic integration of the available data), this third part is more like an interpretation (an integrative inference based on psychoanalytic principles that considers unconscious fantasies and motives). As in the clinical situation, this interpretation is of necessity speculative, a hypothesis that will be tested and modified by additional data. Unlike the clinical situation, though, this interpretation is primarily a guide for the therapist; in most instances it does not directly represent what the patient will be told.

This section of the formulation is most useful clinically if it does not attempt to explain too much in too many ways but instead focuses on the central conflicts and then uses prototypic psychodynamic models to explain how these conflicts are being resolved. The danger of not focusing on the central conflicts and of not using standard psychodynamic models is that the formulation (and consequently perhaps the treatment itself) will lack an integrative coherence.

Identifying the central conflicts requires both inductive and deductive reasoning. The aim is to find a small number of pervasive issues that run through the course of the patient's illness and can be traced back through his or her personal history, and then to explain how the patient's attempts to resolve these central conflicts have been both maladaptive (producing symptoms and character pathology) and adaptive (characterizing his or her general style of pleasure, productivity, and personal relationships). Conflicts are opposing motives and wishes, both conscious and unconscious; central conflicts are repetitive, link and explain a number of important behaviors, and usually contain elements that are hidden from the patient's awareness. For example, a man may consciously wish to be less depressed but unconsciously fear that recovery will both lead to an uncontrolled expression of his own rage and free others to express their resentment against him if he is not protected by illness.

Once the central conflicts and themes have been identified, they are formulated psychodynamically. At present, at least three models of mental functioning are being used by dynamic psychiatrists. These models are overlapping and differ in the emphasis they give to one or another aspect of development and psychopathology. In practice, most psychiatrists prefer one model, on the basis of prior training and personal predilection, but use other models as the clinical situation may require. If the original model does not seem to be conceptually useful, the therapist sees if the formulation of a given patient will be more fruitful when cast in terms of an alternative model. As with many other sciences, the absence of a meta-model to explain all data makes this trial and error unavoidable.

Even though an admixture of different models is often clinically necessary, it is useful theoretically and conceptually to understand the basic concepts, virtues,

and limitations of prototypic psychodynamic models. Recognizing the oversimplification involved, we will describe the three most common: 1) ego-psychological (9); 2) self-psychological (10); and 3) object relations (11, 12). They all share the core concept of dynamic unconscious mental activity; that is, they assume that human behavior is constantly influenced by unconscious thoughts, wishes, and mental representations. These three models also assume that complex psychological functions pass through a regular sequence of epigenetic stages and phases (each of which carries its own particular vulnerabilities and opportunities and involves an interaction between nature and nurture) and that the distortions, fixations, and regressions occurring at different stages will leave their mark on later development. In short, these models assert that all individuals have an inner life that is important in understanding their outer life and that they are each the product of their personal history.

The ego-psychological model emphasizes the central role of the adaptive efforts of the ego both during development and in therapy. Behavior, mediated by the ego, is viewed as a defensive compromise among 1) wishes and impulses; 2) inner conscience, self-observation, and criticism; and 3) the potentialities and demands of reality. Effective ego functions allow an appropriate delay between peremptory wishes and actions and protect the individual from excessive anxiety or depression while providing for security, pleasure, and effectiveness. A dynamic formulation that uses this model will describe the nature of unconscious wishes, unconscious fears, characteristic defenses, and the resulting patterns of inhibition, symptoms, and character, tracing each of these through the individual's life. The ego-psychological model gives special focus to derivatives of forbidden sexual and aggressive strivings, their resolution during the oedipal phase, and the ongoing residual intrapsychic conflicts and defensive compromises that determine character and symptoms. This model gives less attention to interpersonal issues and to very early, pre-oedipal influences on development.

The self-psychological model postulates a psychological structure, the self, that develops toward the realization of goals that are both innate and learned. Two broad classes of these goals can be identified: one consists of the individual's ambitions, the other of his or her ideals. Normal development involves the child's grandiose idealization of self and others, the exhibitionistic expression of strivings and ambitions, and the empathic responsiveness of parents and others to these needs. Under these conditions, the child's unfolding skills, talents, and internalization of empathic objects will lead to the development of a sturdy self and capacities for creativity, joy, and continuing empathic relationships. In this model, genetic formulations will trace character problems to specific empathic failures in the child's environment that distorted and inhibited the development of the self and the capacity to maintain object ties. The formulation will also describe how the individual has defensively compensated for these failures of self-development and will suggest the therapeutic strategy needed to support the resumption of self-development that had been arrested in the past, emphasizing the special transference needs of the patient. The self-psychological model is especially useful for formulating the narcissistic difficulties that are present in many types of patients (not just narcissistic personality disorder); however, the model lacks a clear conception of intrapsychic structure, and it is less useful for formulating fixed repetitive symptoms that arise from conflicts between one's conscience and sexual-aggressive wishes.

The object relations model conceives of psychic structures as developing through the child's construction of internal representations of self and others. These representations range from the primitive and fantastic to the relatively realistic; they are associated with widely varying affects (e.g., anger, sadness, feelings of safety, fear, pleasure) as well as with various wishes and fantasies (e.g., of sex, of control, or of devouring and being devoured). The growing child struggles with contradictory representations and feelings of self and others, tending to split the good and bad images into different representations. At this early level of development, one may feel that one has two different mothers, for example—a good, gratifying one and a bad, frustrating one. In the more mature individual, these images are integrated into coherent representations of a self and others with multiple complex qualities, selected and formed in part to help to maintain an optimal measure of self-esteem, tolerable affects, and satisfaction of wishes.

Using this model, the psychodynamic formulation focuses on the nature of the self and object representations and the prominent conflicts among them. A special emphasis is given to developmental failures in integrating the various partial and contradictory representations of self and others and to the displacement and defensive misattribution of aspects of self or others. The object relations model is especially useful for formulating the fragmented inner world of psychotic and borderline patients who experience themselves and others as unintegrated parts; however, the model may be less useful for relatively healthier patients in whom conflict may more easily be described in terms of ego psychology.

Part 4: Predicting Responses to the Therapeutic Situation

This final section of the formulation is related to the prognosis, but rather than predicting the overall course of the patient's disorder, it focuses on the meaning and use that the patient will make of treatment. Particular emphasis is placed on understanding the probable manifestations of transference (both positive and negative) and the forms and modes of resistance. The phrasing of this prediction will be linked to the psychodynamic model used in the preceding section.

For example, the ego-psychological model may emphasize what specific ego strengths and deficits the patient brings to the therapeutic situation and what defense mechanisms are likely to predominate as the patient deals with central conflicts. The self-psychological model will emphasize the role of the therapist's empathic responsiveness and the analysis of empathic failures in the process of forming new internal structures of the self—for example, the patients' needs to idealize either themselves or the therapist or, at other times, to ignore the therapist except as a source of admiration for exhibitionistic strivings. Finally, the object relations model will emphasize which inner representations of self and of others are likely to be activated and potentially enacted in the therapeutic situation. All three models suggest possible patterns of transference and resistance, offering valuable guides for the therapist.

SAMPLE PSYCHODYNAMIC FORMULATIONS

Although the following psychodynamic formulations lack the authenticity, specificity, and richness of a formulation that is accompanied by a fuller knowledge of the individual history, they are intended to convey something of the format of prototypic dynamic formulations. The same patient is used to illustrate each of the psychodynamic models described previously. These illustrations are admittedly somewhat artificial because, as we have indicated, in clinical practice therapists tend to use one primary model, introducing secondary models to explain features of the patient that do not easily fit the primary model. However, by presenting each of the models in its pure form, we hope to demonstrate the common utility of all the models as well as highlight the potential and unavoidable impact of theory on treatment.

The Ego-Psychological Model

Part 1: Mr. A, a 52-year-old married businessman, presents on his own initiative with a depressive syndrome after being once again passed over for promotion. He himself does not understand this "rejection," but it is probably related to his lifelong tendencies to procrastinate and to annoy his superiors either by being obsequious or by challenging their authority. He has a history of two untreated depressive syndromes, one in his 30s that also followed a professional failure and one in his 40s that followed his son's "defiant" marriage to a woman of another religion. Mr. A's father was a sickly, professionally frustrated "type A personality" who died of a heart attack when Mr. A was in his teens. His mother has always been a "martyr" with smoldering despair characterized by chronic insomnia, self-doubt, obsessive ruminations, and social withdrawal. She never sought treatment.

Part 2: Mr. A has essential hypertension, for which he takes methyldopa, 250 mg t.i.d.; his mother's history suggests a genetic predisposition to unipolar depression.

Part 3: Mr. A's central conflict is between an unconscious wish to kill off his competitors and an unconscious fear that he will be killed if he acts on that wish. Whenever he expresses derivatives of his competitive wish directly, he becomes frightened of retaliation; he therefore resorts to expressing the wish indirectly by passive-aggressive maneuvers (e.g., procrastination). Conversely, whenever he responds to this fear of retaliation by being solicitous and obedient, he inwardly feels resentful and diminished. To contain this struggle, Mr. A has developed intellectual mechanisms that, although adaptive for certain aspects of his work, are maladaptive interpersonally in that they isolate him emotionally from others.

Mr. A's tendency to view every situation as a competitive struggle can be traced to unresolved anal and oedipal conflicts. During early childhood, Mr. A's depressed mother could not tolerate her son's assertiveness and declarations of independence; instead she imposed her will on Mr. A and insisted that he eat, sleep, be toilet trained, and behave exactly the way she wanted so that her son would not be any trouble and add to her woes. As a result, Mr. A entered the oedipal period with a view that any endeavor was a power struggle, in essence asking himself, "Do I give in and bury the rage over being controlled, or do I assert myself and risk being punished either directly by my mother or internally by the guilt I feel by making her more depressed?"

This view of the world was then enhanced by competition from Mr. A's perfectionistic and controlling father, who, frustrated by his own limitations and illness, would harshly reprimand Mr. A for any assertion within the family or failure outside of it. Fearing retaliation and struggling against his feelings of passivity, Mr. A identified with the aggressor-father and developed an even more punitive superego. Mr. A's need to repress his competitive rage and envy was reinforced by his father's chronic heart disease; Mr. A feared that if he were to act assertively, he would kill off his rival. When the father did die during Mr. A's adolescence, the guilt over this unconscious oedipal victory made Mr. A even more wary of directly asserting himself in the future. All three of Mr. A's depressive episodes were precipitated by failing to beat out competitors (colleagues or his son), unconsciously reminiscent of earlier defeats with his mother and father, but Mr. A is unaware that he is equally afraid to win and face the resultant retaliation and guilt.

Part 4: Unconsciously Mr. A is likely to view treatment as another competition. Fearful and dependent at first, when his depression begins to improve and he feels more like a "winner," he may respond with guilty fear for a triumph so undeserved in one who unconsciously is consumed with murderous wishes. In response to this guilt, he may sabotage his improvement by prematurely stopping treatment or, less destructively, by focusing on residual depressive

symptoms, the side effects of antidepressant medication, or his hypertension (an affliction that unconsciously has become his punishment for killing his father). This behavior will alternate with Mr. A's viewing the therapist as the winner (i.e., the authority figure to whom he is beholden). Frightened of challenging the victor directly, Mr. A may indirectly defy this authority by appearing compliant, apologetic, and grateful but passive-aggressively "forgetting" appointments or his medication and devaluing the treatment.

The Self-Psychological Model

Parts 1 and 2 are as in the previous material.

Part 3: Mr. A's central problem consists of his low self-esteem and consequent need for continual recognition and approval from others, along with his inability to accept any limitations either in himself (which lead to disapproval from others) or in others (which reduce the value of their approval when it occurs). Presumably, during childhood his depressed mother and sickly father were so self-absorbed with their problems that they were unable to respond empathically to his age-appropriate aspirations; at the same time, both parents narcissistically invested in their son the hopes that his achievements would make up for their failures. Throughout his life Mr. A has strived to earn the accolades he never received as a child, and although this pursuit has lead to some professional success, his self-doubt and instability of self-objects take their toll, leading to a lack of confidence, to inappropriate solicitous behavior, and to procrastination of challenging tasks. In addition, having internalized his parents' grand expectations (in order to repair his sense of deficit as well as to compensate for theirs), he is unable to accept the limitations of others (e.g., his bosses' or his son's) or himself (e.g., physical illness, aging, his professional plateau). Being passed over for promotion was an injury to a sense of self that was already enfeebled; the rejection reawakened early empathic failures and unrealized ambitions. The resultant loss of self-esteem then contributed to the current depression.

Part 4: In treatment, Mr. A will attempt to elicit the therapist's admiration and will have grand (though unconscious) expectations about what can be accomplished, idealizing both himself and the therapist. However, when the therapist fails to respond with just the right empathic quality, Mr. A will be hurt and secretly enraged, and when the real limitations of Mr. A or the therapist are exposed, Mr. A is likely to devalue the entire enterprise and become more discouraged. Potential countertransference problems may arise if the therapist prematurely limits Mr. A's need to be admired and to idealize the therapist.

The Object Relations Model

Parts 1 and 2 are as in the earlier material.

Part 3: Mr. A's central problem is his failure to integrate the good and bad representations of himself and others. During childhood, his depressed mother could not respond to her son's need and demands. Mr. A, unconsciously frightened that his resultant rage would destroy the very one on whom he depended, repressed his bad angry self and acted like the good obedient son. This splitting was reinforced by interactions with the controlling father who punitively viewed any of Mr. A's independent assertions as acts of defiance. Mr. A, frightened that his competitive rage would either kill off the sickly father or lead to retaliation, again repressed his bad angry self. During adolescence, when the surge toward a more autonomous identity was most intense, Mr. A's father died. Responding to unconscious guilt for a forbidden wish that had come true (i.e., killing off the father), Mr. A was even more compelled to keep the bad (assertive) self repressed and to maintain a tie to the lost object, both by an identification with the father's perfectionism, and to punish himself for any success. Although this splitting has enabled Mr. A to be relatively successful and to seem basically well intentioned, the facade is fragile. The efforts with his superiors to appear "the good son" are exaggerated, leading to obsequious and subservient behavior. Furthermore, when the bad angry self breaks through the repression, procrastination and obstinacy are the result. These signals of the bad self lead to increased self-punitive and restrictive reactions in order to keep his rage contained.

Mr. A's repression and splitting are compounded by his use of projection; that is, he projects onto others his unconscious bad self. This process only reinforces his experience of others as either unnurturing mothers or unsupportive, controlling fathers. This projection of the bad self contributed to Mr. A's viewing his son's marriage as an act of defiance. Similarly, when passed over for promotion, Mr. A not only experienced this rejection as reminiscent of enraging childhood rejections, devaluations, and abandonment but also viewed it as a retaliation for projected hostile wishes from his bad self. His depression is therefore in part the result of his punitive conscience condemning him for projected hostile wishes and for failing to meet the perfectionistic ideals of the good self.

Part 4: In treatment Mr. A will at first be quite ingratiating, the good son depressively condemning himself for past and present failures and wary that he will not meet the therapist's expectations (Mr. A's own projections). However, as Mr. A projects his resentful and defiant self, the therapist may be perceived as being both emotionally uncaring and as controlling, projections that will reinforce in the transference those early experiences with the mother and father, respectively. The therapist should be prepared for the likelihood that Mr. A's rise in self-esteem will initially be accompanied by denigration of the therapist. The therapist must also anticipate that whenever Mr. A does express the resentful affects associated with the bad self, Mr. A's conscience will clamp down puni-

tively and cause Mr. A to become temporarily more depressed.

CLINICAL APPLICATION OF THE FORMULATION

Although there are differences among the three formulations, it is important to point out the similarities in their clinical conclusions and applications. All three formulations alert the therapist that after an initial honeymoon period, difficulties are likely to develop in the therapeutic relationship. The ego-psychological model conceives of this falling out in terms of passive-aggressive defensive mechanisms, the self-psychological model predicts a devaluation of the therapist in response to inevitable empathic failures and limitations, and the object relations model anticipates that the patient's angry and defiant self will be projected onto the therapist.

All three formulations also alert the therapist to similar countertransference problems: the ego-psychological model places these problems in terms of competitive struggles with the patient over issues of control, the self-psychological model considers problems of the therapist's being initially idealized and then devalued, and the object relations model suggests that the therapist may at times feel compelled to identify with the patient's projections and then assume the role of the uncaring and punitive figure the patient most fears and expects.

All three formulations indicate that the patient's dynamics may directly affect his depressive symptoms and compliance with whatever treatment is prescribed. The ego-psychological model views this resistance in terms of guilty fear accompanying his improvement and a need to indirectly defy authority. The self-psychological model predicts a phase of discouragement and unwillingness to accept the disappointing therapy. The object relations model foresees that depressive feelings may recur if this patient retreats from the emergence of his angry bad self during recovery and that poor compliance will accompany the view of the therapist as punitive and uncaring.

Finally, all three formulations share many similarities in indicating what therapeutic interventions will be required to manage the anticipated transferences, countertransferences, and resistances. They all see that this patient in particular will need a nonjudgmental atmosphere where anger and resentment can be expressed spontaneously, he will need appropriate recognition and reinforcement of his strengths (such as his intellectual capacities), and he will need a modicum of control in his treatment (such as deciding within reason the time of day he takes his medication).

Despite these basic similarities, the different conceptual models will no doubt have some influence on the treatment's emphasis and language. We suspect that these differences would be most apparent in the nature of interpretations used in an exploratory psychotherapy and less apparent in directive, behavioral, supportive, or psychopharmacological treatment. Using the ego-psychological model, the therapist is likely to focus on the relationship between the patient's current difficulties and earlier competitive struggles with his parents. Using the self-psychological model, the therapist will direct interpretations toward helping the patient appreciate the doubts and yearnings that underlie his fragile grandiosity and will trace perceived empathic failures in the therapist to those failures that occurred in the patient's childhood. Finally, using the object relations model, the therapist will attempt to intercept a destructive negative transference and acting out both by interpreting the patient's misperceptions of the therapist as someone (like the father) wanting to control the patient and by encouraging the patient to express through fantasies, memories, and dreams those angry feelings associated with the bad self, thereby indicating a capacity (unlike the mother) to tolerate unpleasant affects.

However, in closing, it must be emphasized that the differences that may occur in an insight-oriented psychotherapy are relatively subtle compared to the more important value of the psychodynamic formulation in conceptualizing central conflicts and anticipating the transferences, countertransferences, and resistances that occur in all treatments.

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Psychiatric Aspects of AIDS

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Acquired immune deficiency syndrome (AIDS) has neuropsychiatric and psychopathological complications: anxiety, depressive symptoms, and suicidal ideation are common. Patients may express anger toward ineffective medical care and perceived public discrimination, guilt about sexual practices or drug abuse, reactions to social isolation, and uncertainty about the implications of an AIDS diagnosis. CNS dysfunction and subsequent neuropsychiatric impairment are common and are initially characterized by decreased acuity, slowed mentation, and psychomotor retardation that can resemble depression. Marked global cognitive deficits, disorientation, and delusions ensue. The author discusses case management and outlines future clinical and research activities.

(Am J Psychiatry 1987; 144:551–556)

The acquired immune deficiency syndrome (AIDS) is characterized by a profound disturbance in cell-mediated immunity that afflicts previously healthy individuals. Its incidence has steadily increased since the early 1980s, and it has thus emerged as a serious public health problem (1, 2). This article is an overview of the current knowledge concerning the manifestations and psychiatric aspects of AIDS.

Currently, the major high-risk group comprises homosexual and bisexual men with multiple sexual partners, who account for approximately 70% of all reported AIDS cases (3). The group with the next highest prevalence is users of illicit intravenous drugs, who constitute approximately 15%–20% of the total AIDS cohort (3, 4). Additional high-risk groups include hemophiliacs receiving factor VIII concentrate (3, 5, 6), children of high-risk individuals (3, 7), and the female sexual partners of men with AIDS (3, 8, 9). It should be noted that there have been reports of female-to-male transmission (10, 11), but more data on this issue are needed.

AIDS is generally considered to be caused by a newly discovered retrovirus termed human T cell lymphotropic virus type III/lymphadenopathy-associated virus, i.e., HTLV-III/LAV (12–15). The available evidence suggests that HTLV-III/LAV transmission occurs only through bodily fluids and usually involves sexual contact, transfusion of blood or blood products, use of syringes contaminated with HTLV-III/LAV, or transmission from infected mothers to newborns (16, 17). This virus does not appear to be easily transmitted through casual contact with an infected individual (18). In this regard, the Centers for Disease Control (CDC) (19) have concluded that there is only a low risk of HTLV-III/LAV transmission from patients to health care workers. Parenthetically, a very small number of documented cases among health care workers exhibiting no other risk factors may have been caused by injuries with contaminated needles (19). In general, the CDC guidelines (19) for preventing transmission emphasize avoidance of direct exposure to infected individuals' blood or other bodily fluids (20).

Enzyme-linked immunosorbent assay (ELISA) is usually the initial screening instrument employed to detect HTLV-III/LAV antibodies. Positive ELISA results, according to the standard protocol, are checked with a repeat test using the same specimen. Repeatedly positive ELISA results are followed by the Western blot assay to specify the actual presence of HTLV-III/LAV (21–23). Approximately 1,500,000 Americans have HTLV-III/LAV antibodies (CDC, personal communication, 1987). According to projected estimates from the CDC, the percentage of persons with HTLV-III/LAV antibodies who will eventually develop AIDS over the next several years ranges from 25% to 50%. A complicating factor in this area of research is the unknown latency period between infection and the time of AIDS manifestation.

DISEASE MANIFESTATIONS

The onset of AIDS is related to a significant reduction in the ratio of helper to suppressor T lymphocytes (24–30). As such, this immunosuppressive syndrome can be manifested by the development of Kaposi's sarcoma, high-grade lymphomas, and multiple opportunistic infectious agents involving protozoa (*Pneumo-*

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The author thanks Carolyn Farineau and Kim Hutchinson for their assistance in this project.

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cystis carinii, Toxoplasma gondii), fungi *(Cryptococcus neoformans, Candida albicans),* bacteria *(Mycobacterium avium-intracellulare),* and viruses (cytomegalovirus, herpes simplex) (31, 32).

The initial symptoms of AIDS generally include persistent generalized lymphadenopathy, shortness of breath and coughing, yeast infections, fatigue, recurrent diarrhea, and unexplained weight loss. In some cases, symptoms of depressive illness may antedate these other prodromal symptoms. The diagnosis of AIDS is not applied unless the presence of a disease indicative of immune deficiency is established (20, 33). For instance, *Pneumocystis carinii* pneumonia is the most common disease in AIDS patients, representing approximately 60% of the initial diagnoses in these patients (34). It typically involves the gradual onset of a nonproductive cough, low-grade fevers, and generalized chest pain (35). Also, Kaposi's sarcoma is diagnosed in a significant percentage of AIDS patients (28, 36); among AIDS patients this cancerous disease is particularly virulent and rapidly spreads to the lymph nodes and internal organs. Survival time after the diagnosis of Kaposi's sarcoma is usually less than 2 years (34, 37). Individuals who do not meet diagnostic criteria for AIDS but test positive for HTLV-III/LAV antibodies and exhibit some clinical signs of AIDS are frequently described as having AIDS-related complex. This syndrome has not been completely defined and may encompass several HTLV-III/LAV diseases (20, 24, 38).

There is no effective treatment for the underlying immune deficiency of AIDS. Traditional approaches such as chemotherapy and radiation have been employed with some success in treating lymphomas and Kaposi's sarcoma; however, the lethal immunosuppressive condition remains unaffected by these procedures. In spite of aggressive and consistent medical care, most patients experience rapid deterioration, resulting in death within 24–36 months, and those with the best prognosis usually die within 5 years (38). Several drug trials are presently being conducted in an attempt to inhibit reverse transcriptase, since this enzyme is necessary for replication of HTLV-III/LAV. Drugs currently studied include azidothymidine (AZT), suramin, HPA-23, trisodium phosphonoformate, ribavirin, ansamycin, and interferon (39–42). These chemical agents are considered to inhibit reverse transcriptase activity and thus may prevent HTLV-III/LAV replication (39–42). Much empirical attention is also being concentrated on the prospects for development of an AIDS vaccine (26). Research on these drug treatments and vaccines is in the early stages, and there is no indication of when effective agents can be expected.

PSYCHIATRIC AND PSYCHOSOCIAL IMPLICATIONS

It has become apparent that psychiatric complications commonly occur during the clinical course of AIDS (43). These complications have been manifested by neuropsychiatric and psychopathological symptoms. In addition, significant psychosocial stress has resulted from ambivalent or even negative societal reactions, especially toward the predominant high-risk group of homosexual men. The following is an integration of the available information on psychiatric complications in AIDS patients and implications for case management and future research.

Distress of the "Worried Well"

Homosexual and bisexual men and users of intravenous drugs are at particularly high risk for AIDS. Many of these individuals who have not had symptoms of AIDS or AIDS-related complex can be considered part of the "worried well." That is, these persons realize their life styles have put them at risk for disease onset, and they are concerned about developing AIDS. Although asymptomatic, many of these individuals consequently have significant psychological distress. In general, these symptoms are anxiety-related and include panic attacks and generalized anxiety (44–46). Similarly, symptoms of obsessive-compulsive disorder and hypochondriasis can occur, e.g., excessive somatic preoccupation and fears of the disease (44–46). Some concern also may be developing in heterosexual individuals with multiple sexual partners because of the apparent possibility of heterosexual transmission. This concern may be more prevalent in heterosexual partners of individuals in high-risk categories. Although some reactions of the "worried well" may be within normal limits, some of these individuals suffer from sufficient distress to severely disrupt social and occupational functioning. Thus, this population requires increased clinical and research attention from the psychiatric community.

Psychiatric Symptoms

Many of the psychiatric symptoms that develop after diagnosis of AIDS or AIDS-related complex are similar to those reported in patients with terminal cancer (45, 47). At diagnosis, patient reactions are typified by denial and disbelief, which are followed by depressive and anxiety symptoms (48, 49). Feelings of hopelessness and fearful uncertainty can be expected, and suicidal ideation in AIDS patients may occur as the disease progresses. The anxiety symptoms may include agitation, panic attacks, anorexia, tachycardia, and insomnia. Intense anger is common and is generally directed toward ineffective medical care, perceived public discrimination, and/or displeasure with governmental responses to the epidemic. Patients with AIDS-related complex probably do not take solace in the fact that AIDS has not been diagnosed and likely live in fear of eventually developing the full-blown syndrome. In sum, the characteristic stress response found after AIDS, and perhaps AIDS-related complex, is diagnosed is comparable to that of terminal cancer, creat-

ing similar levels of emotional distress and raising the same set of existential issues (50).

There have been some detailed reports of psychiatric consultations with AIDS patients. Dilley et al. (51) found that of the 40 inpatients seen at San Francisco General Hospital by the time of their report, 13 had been referred to the psychiatric consultation-liaison service. "Depression" was the primary reason for referral in a majority of these cases. Twelve of the 13 patients received psychiatric diagnoses. The most common *DSM-III* diagnosis was adjustment disorder with depressed mood (N=7), followed by major depression (N=2), dementia (N=1), delirium (N=1), and panic disorder (N=1). Recurrent psychological themes observed during the diagnostic and follow-up interviews were uncertainty about the implications of an AIDS diagnosis, social isolation, dealing with a life-threatening illness, and guilt over previous life style. Other studies (49, 52) have reported that psychiatric consultations for AIDS patients primarily concern depressive symptoms, suicidal risk, and neuropsychiatric impairment. Overall, the limited clinical observations suggest that suicidal ideation is common but that actual attempts are not prevalent, and self-destructive behavior tends to be more probable in AIDS patients with personality disorders, particularly the borderline type (49).

CNS Complications

As the disease progresses, approximately 30%–40% of AIDS patients present signs and symptoms of CNS dysfunction, and around 80% exhibit post-mortem neuropathological abnormalities (53–57). These CNS defects are generally associated with neuropsychiatric symptoms. The most commonly reported CNS dysfunction in AIDS is a nonfocal encephalopathy (56–58). Snider et al. (57) reported what they considered to be subacute encephalitis in 18 of 50 AIDS patients. Symptom onset was characterized by malaise, social withdrawal, lethargy, and reduced sexual drive. Anorexia and diarrhea resulted in significant weight loss for several patients. Over several weeks to months, the patients exhibited symptoms of a progressive dementia, including psychomotor retardation, incontinence, confusion, and in some cases, occasional hallucinations. Analyses of CSF revealed that 12 of 16 patients had mild pleocytosis, protein elevation, and/or lowered glucose levels. CAT scans showed generalized cerebral atrophy in 10 of 13 cases.

Nielsen et al. (56) also found a high prevalence of this subacute encephalitis, identifying 19 of 40 AIDS patients as having this dementing illness. Similar to patients described by Snider et al. (57), these patients were initially withdrawn and lethargic and developed marked psychomotor retardation and, eventually, dementia. Diffuse cerebral atrophy was identified by means of CAT scan. An etiologic agent of the subacute encephalitis was not identified, but Nielsen et al. speculated that the histopathology implied an association between a cytomegalovirus-type infection and the clinically observed dementia. Likewise, others (57, 59) have conjectured about the possible etiologic role of cytomegalovirus infection. Furthermore, DNA infected with HTLV-III/LAV was observed in five of 15 brains from patients with this AIDS dementia (60). This finding has generated questions regarding the similarities between HTLV-III/LAV and visna virus, since the latter causes CNS degeneration in sheep (61). Although not as prevalent, well-defined focal lesions have also been observed in AIDS patients with progressive multifocal leukoencephalopathy, toxoplasmosis, associated cerebral vascular complications, and meningeal and primary cerebral lymphoma (53, 56, 57). In general, the subacute encephalitis or subcortical dementia appears to be the most frequent CNS complication and can be pathologically characterized by neuronal loss, cerebral atrophy, glial nodules, and microfocal demyelination (49).

Neuropsychiatric deficits are frequently related to these CNS complications in AIDS. Tross et al. (62) evaluated over 180 AIDS patients, and more than 50% eventually developed neuropsychiatric impairment. These deficits included impaired language, memory, and integrative abilities. However, the demonstrated CNS abnormalities have not precisely correlated with the degree of cognitive dysfunction or dementia (55, 57, 60, 63). Nonetheless, several reports (59, 64–66) have concurrently cited CNS involvement and documented neuropsychological sequelae. These investigators primarily discerned diffuse cerebral atrophy and employed neuropsychological testing to evaluate consequent cognitive dysfunction. This series of case studies and the results of other investigations (57, 60, 62) yield a general clinical pattern. Initially, patients with AIDS dementia appear to be psychologically depressed and to have blunted affect, impaired memory, poor concentration, and social withdrawal. Hence, psychiatric consultation may be initiated at this relatively early stage of the disease. At this time consultation-liaison services should aggressively assess these high-risk patients to determine their neuropsychological deficits and CNS involvement. Over several months, patients eventually become severely delusional and disoriented, demonstrating marked global cognitive deficits. This insidious disease can gradually result in seizures, mutism, and coma. In sum, neuropsychiatric sequelae of CNS complications in AIDS probably represent a type of subacute encephalitis or subcortical dementia, but precise neuropathological mechanisms have not yet been identified (67). I have reviewed these CNS complications elsewhere (67).

Societal and Medical Staff Reactions

The intense media coverage of AIDS has increased public scrutiny of the life styles of homosexual men and intravenous drug abusers. It is possible that where negative societal reactions already exist, such reactions could be further strengthened by holding these groups

somehow responsible for "their" disease. Moreover, high-risk individuals, and even AIDS patients who are neither gay nor drug abusers, may be socially ostracized and blamed for further public contagion. Clearly, the precise mechanisms of disease transmission have not been delineated for all cases. Nevertheless, there appears to be a distinct discrepancy between public health guidelines and the behavioral response of the public (68, 69). Thus, precautions and preventive measures specified by organizations such as the American Council on Science and Health (42) may be disregarded by the public in favor of more discriminatory and prejudicial actions. The perceived stigma of AIDS may not only result in discriminatory behavior but could weaken patients' social support systems, potentially increasing their vulnerability to disease progression (70–72).

In addition to societal reactions toward AIDS, the attitudes and responses of medical staff are also important considerations (Massie and Barbuto, unpublished report, 1984). Medical personnel must admit and confront their own concerns about AIDS, perhaps involving unfounded beliefs about modes of disease transmission or negative attitudes toward caring for homosexuals and drug abusers. Many potential problems can be circumvented by providing hospital staff with current information regarding proper safety precautions and encouraging the rational confrontation of negative attitudes. The goal of these measures should be to prevent any interference with optimal patient care. Also, the unique stresses of dealing with fatal diseases can adversely affect medical staffs (73). Frustration and grieving due to the inability to successfully treat AIDS can be anticipated and should be appropriately expressed.

IMPLICATIONS FOR MANAGEMENT OF AIDS PATIENTS

In view of the common psychiatric and CNS sequelae in AIDS, monitoring of mental status and cognitive deficits should become an integral part of the overall management of AIDS patients. Depressive symptoms and suicide risk should be assessed. Supportive psychotherapeutic approaches should involve issues such as guilt associated with sexual practices or drug abuse, possible social isolation, and acknowledgment of the illness and any associated fear or anger. Provision of stress-management and problem-solving procedures could also be of benefit to these patients. Moreover, benzodiazepine and antidepressant therapy may be considered for alleviation of excessive anxiety and depressive reactions. Some investigators have preferred the short-term use of antianxiety medication as the initial drug of choice instead of antidepressants (74, 75), and behavioral stress reduction techniques have also been advocated (45).

The potential for CNS involvement should always be considered. In the early stages of AIDS, neuropsychiatric symptoms of CNS defects may clinically appear as psychological depression. Therefore, neuropsychological testing could be helpful in differential diagnoses. Particular attention should be given to patients with treatable CNS infections in an attempt to obviate neuropsychiatric sequelae.

Patient management should also include dissemination of the most recent updates on AIDS, information on etiology and modes of transmission, and practical precautions regarding safer sexual practices and needle use by drug abusers. A series of community-based behavioral interventions have been suggested (76) that may be effective in primary prevention. If available, referrals to local AIDS outreach organizations can also be useful in buttressing social support. In addition, public health agencies may help patients obtain financial and physical assistance.

FUTURE EFFORTS

It is probably accurate to assume that AIDS, as both a health problem and social issue, will continue to receive high visibility throughout this century and perhaps beyond. Hence, there is a need for extensive discussion and consideration of potential legal and public health policy issues, such as job discrimination. In addition, systematic research efforts are needed to address the refinement of psychiatric assessment and treatment in AIDS. There is a need for empirical observations of factors associated with delay in seeking treatment, the role of psychosocial stress in disease onset and maintenance, psychological effects on and needs of family members, and psychiatric factors predicting length of survival. As a model for these future research efforts, an established data base is available from investigations on psychiatric aspects of cancer, in which adaptive coping styles have been identified (47, 77–79, and unpublished 1981 report of Greer and Morris). AIDS poses a significant challenge to the mental health profession in general and psychiatry in particular; thus, increased attention to this disease is needed from both clinical and research perspectives.

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Use of ECT in the United States in 1975 and 1980

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The authors examined data from the National Institute of Mental Health regarding the use of ECT in the United States in 1975 and 1980. A total of 33,384 hospitalized patients were treated with ECT in 1980, representing 2.4% of all patients hospitalized in psychiatric facilities. The use of ECT decreased by 46% between 1975 and 1980. Of the type of facilities surveyed, only public general hospitals did not decrease their use of ECT. Patients with affective disorders received 69.8% of the ECT given, and patients with schizophrenia received 16.6%. Although more women than men received ECT, diagnosis and age were more important factors than sex.

(Am J Psychiatry 1987; 144:557–562)

The literature on the clinical use of ECT is quite large (1–4). The literature on the patterns of delivery of this treatment in the U.S. service system is less extensive, however (5–10), and studies have often been limited by the use of a sample that is not representative or by a focus on a single type of facility, one geographic area, or a single point in time. It is the purpose of this paper to present national estimates of ECT use in the United States, based on a representative sample of hospitals and patients over time.

Weiner and Power (5) found that of all patients in Veterans Administration (VA) hospitals in 1977, 79% were depressed and 21% were schizophrenic. They also found that 0.21% of the patients with schizophrenia and 3.1% of the patients with depression in VA hospitals received ECT. In contrast, a study by Hedlund et al. (6) showed that 9.1% of the patients with schizophrenia and 10% of the patients with depression in state hospitals in Missouri between 1971 and 1975 received ECT. Morrissey et al. (7) reported a decrease over time in the use of ECT in New York State; they found that it was used primarily in the private sector.

Babigian and Guttmacher (8), using the psychiatric case register of Monroe County, N.Y., from 1961 to 1975, found that the prevalence of ECT use decreased over the study period and that patients receiving ECT tended to have an affective disorder and to be female, over 45 years old, and from the middle or upper socioeconomic class.

Mills et al. (9) showed that use of ECT in Massachusetts decreased in state hospitals and to some extent in other facilities between 1974 and 1980. Kramer (10), however, indicated that in spite of limitations in the availability of ECT, there had been little change in the number of patients receiving ECT in California between 1977 and 1983.

In a national survey of psychiatrists (11), APA estimated that of 88,604 patients who had received ECT during 1976 (41.3 per 100,000), 82% were depressed and 17% were schizophrenic.

Smith and Richman (12) reported that ECT use in Canada decreased from 35.6 per 100,000 in 1969 to 29.9 per 100,000 in 1978. Pippard and Ellam (13) reported statistics for Great Britain that translate into a rate of 56.6 per 100,000 in 1979, a 50% decrease since 1972.

METHOD

The data used in this study are national estimates derived from the Sample Survey Program of the National Institute of Mental Health (NIMH) for 1970, 1975, and 1980. These surveys are conducted as part

Preliminary version presented at the NIH/NIMH Consensus Development Conference on ECT, Bethesda, Md., June 1985. Received Dec. 17, 1985; revised Aug. 13 and Nov. 18, 1986; accepted Jan. 13, 1987. From the Division of Biometry and Applied Sciences and the Division of Clinical Research, National Institute of Mental Health. Address reprint requests to Dr. Thompson, Room 18C-14, 5600 Fishers Lane, Rockville, MD 20857.

The authors thank Marilyn Rosenstein and Laura Millazo-Sayre, who were in charge of collecting the data on which this paper is based, as well as Dr. Richard Weiner, who gave helpful comments.

TABLE 1. Use of ECT for Patients Admitted to or Discharged From Four Types of Psychiatric Facilities in 1975 and 1980

	1975						1980					
			Patients Given ECT						Patients Given ECT			
	All Patients				Percent of All Patients		All Patients				Percent of All Patients	
Type of Facility	N	SE[a]	N	SE[a]	%	SE[a]	N	SE[a]	N	SE[a]	%	SE[a]
General hospitals[b]												
Private	376,185	31,085	40,297	4,502	10.7	0.8	436,589	35,827	20,265	2,774	4.6	0.5
Public	139,352	12,952	3,920	794	2.8	0.5	127,372	11,899	6,181	1,050	4.9	0.7
Private psychiatric hospitals[c]	129,832		9,792		7.5		141,209	2,969	3,847	321	2.7	0.6
State and county mental hospitals[d]	385,237	18,697	4,658	746	1.2	0.18	369,049	17,959	1,221	371	0.3	0.1
Total	1,030,606	—	58,667	3,205	5.7	0.6	1,074,279	—	31,514	2,042	2.9	0.5

[a]Absolute standard error.
[b]Those with separate psychiatric units only.
[c]A 100% sample was taken in 1970 and 1975; standard errors are effectively zero. In 1970, 87,397 patients were admitted to those hospitals; 15,537 (17.8%) of these received ECT.
[d]In 1969, 461,569 patients were discharged from these hospitals; 17,150 (3.7%) of these received ECT.

of the NIMH National Reporting Program (14), which usually has an overall response rate of greater than 90%.

The sample surveys are based on a stratified probability design in which a representative sample of patient admissions (or discharges, for general hospitals) is chosen for a representative sample of facilities. For a sample month, patient data are assembled from the medical record. Three months later, other data, such as the types of treatment received during the admission and the primary diagnosis, are collected from the medical record. The data are inflated to represent a year interval.

Diagnoses were collapsed into aggregate categories that are compatible with both *DSM-II* and *DSM-III*. All disorders related to affective disorder were placed into a single category (e.g., schizoaffective disorder was placed in the affective disorder category).

Standard errors for both 1975 and 1980 were derived using SESUDAAN, a computer program developed for computing standard errors from sample survey data that takes into account complex sample design (15, 16). (Although it is *Journal* policy to report standard deviations, in large surveys with complex sample designs the standard error is the appropriate measure of dispersion [15,17].) The figures for private psychiatric hospitals in 1970 and 1975 represent essentially 100% of patients, which means that the standard errors for these figures are effectively zero. Standard errors for all types of hospitals combined are a weighted sum of the standard errors for each individual type of hospital.

Significance levels for totals were determined by using a two-tailed t test with infinite degrees of freedom; significance levels for percentages were determined by using a two-tailed test of the comparison of proportions in independent samples (18). This test produces a standard Z statistic. (Degrees of freedom are not used with the Z statistic.) Regressions were done by using the LOGIST procedure (19), an unconditional logistic regression package compatible with the Statistical Analysis System (20). We did 25 statistical tests and therefore took .002 as our level of significance, following the Bonferroni method of protecting against type I error (21).

RESULTS

When we considered all six types of psychiatric facilities surveyed, we found that 33,384 (2.5%) of 1,335,549 patients received ECT in 1980. Table 1 shows the data for the four types of facilities for which data were available in both 1975 and 1980. There was a 46% decrease in the number of patients receiving ECT in these facilities ($t=7.15$, infinite df, $p<.0001$). There was a 74% decrease in the use of ECT in state hospitals ($t=4.13$, infinite df, $p<.0001$) and a 61% decrease in private psychiatric hospitals ($t=18.52$, infinite df, $p=.0001$). (There was a 75% decrease in use of ECT in private psychiatric hospitals between 1970 and 1980.) There was a 50% decrease in use of ECT between 1975 and 1980 in private general hospitals ($t=3.79$, infinite df, $p<.0005$). Only in public general hospitals did the number of admissions receiving ECT not decrease; the 58% increase did not reach statistical significance ($t=1.72$, infinite df). Private general hospitals accounted for 69% of patients receiving ECT in 1975 and 64% in 1980. Of these four types of facilities, state hospitals used ECT the least in 1975 and in 1980.

The percent of admissions receiving ECT also decreased, from 5.7% to 2.9%, between 1975 and 1980 ($Z=3.59$. $p<.001$). Only in public general hospitals did the percent of admissions receiving ECT not decrease. (The apparent increase was not statistically significant [$Z=2.44$].) The percent of admissions receiving ECT in private general hospitals showed a decline from 10.7% to 4.6% ($Z=6.47$, $p<.0001$). The decrease was significant in state hospitals ($Z=4.47$,

TABLE 2. Diagnoses of Patients Given ECT Admitted to or Discharged From Four Types of Psychiatric Facilities in 1975 and 1980

Type of Facility and Diagnosis	1975 N	1975 SE[a]	1975 %	1975 SE[a]	1980 N	1980 SE[a]	1980 %	1980 SE[a]
General hospitals[b]								
Private								
Affective disorder	30,163	3,645	75.9	3.4	13,015	2,088	64.2	5.4
Schizophrenia	5,636	1,278	14.2	2.8	3,851	1,036	19.0	4.4
Other diagnoses	3,938	1,049	9.9	1.1	3,399	968	16.8	4.2
Public								
Affective disorder	3,177	702	70.9	8.3	5,127	934	83.0	5.5
Schizophrenia	1,053	382	23.5	7.8	414	236	6.7	3.6
Other diagnoses	250	182	5.6	4.2	640	295	10.3	4.4
Private psychiatric hospitals[c]								
Affective disorder	7,454		76.1		3,081	296	80.1	9.2
Schizophrenia	1,595		16.3		565	121	14.7	8.2
Other diagnoses	743		7.6		201	72	5.2	5.1
State and county mental hospitals								
Affective disorder	1,897	465	40.7	7.6	780	295	63.9	14.4
Schizophrenia	1,013	33	21.8	6.3	384	206	31.5	13.9
Other diagnoses	1,748	446	37.5	7.4	57	79[d]	4.6	6.3[d]
Total[e]								
Affective disorder	42,691	2,648	72.8	3.5	22,003	1,505	69.8	6.2
Schizophrenia	9,297	822	15.9	2.9	5,214	812	16.6	5.1
Other diagnoses	6,679	742	11.3	1.6	4,297	814	13.6	4.4

[a]Absolute standard error.
[b]Those with separate psychiatric units only.
[c]A 100% sample was taken in 1975; standard errors are effectively zero.
[d]According to our method, with a very small sample, relative standard errors over 100% are mathematically possible.
[e]Percents are the total number of patients with these diagnoses given ECT divided by the total number of patients with these diagnoses admitted to or discharged from the types of facilities listed.

$p<.0001$) and in private psychiatric hospitals ($Z=7.74$, $p<.0001$).

Several types of facilities were surveyed only in 1975 or 1980. In 1975, outpatient clinics were sampled, and essentially no use of ECT was reported. In 1980, VA hospitals reported that 526 (0.3%) of 158,931 admissions received ECT, and multiservice general hospitals reported that 1,344 (1.3%) of 102,339 admissions received ECT.

The rate per 100,000 of ECT use changed between 1975 and 1980 from 27.5 to 14.7. If only persons over the age of 15 years are included in the denominator, the change per 100,000 is from 36.8 to 19.1.

Diagnosis

The majority of the patients receiving ECT in 1975 and 1980 had affective disorders (table 2). There was no change between 1975 and 1980 in any type of facility or overall in the percent of patients with affective disorder who were given ECT (private general hospitals, $Z=1.83$; public general hospitals, $Z=1.22$; private psychiatric hospitals, $Z=0.44$; state and county mental hospitals, $Z=1.45$; overall, $Z=0.42$).

Only 13.0% (N=42,691) of patients with affective disorder in the four types of facilities were given ECT in 1975. In 1980, only 6.2% (N=22,003) of the patients with affective disorder received ECT, representing a statistically significant change over time ($Z=4.57$, $p<.0001$). An even smaller proportion of patients with schizophrenia were treated with ECT: 3.7% (N=9,297) in 1975 and 2.1% (N=5,214) in 1980). The change over time was not significant ($Z=1.86$).

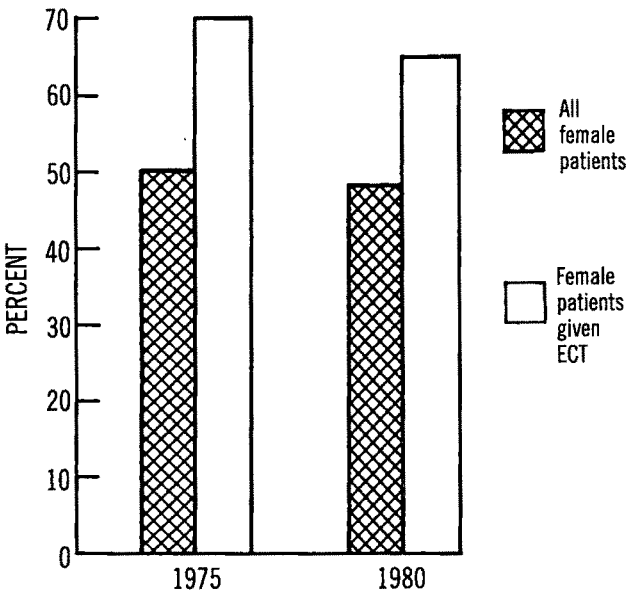
Because we used only primary diagnoses in our calculations, it is possible that for patients in the "other" category (table 2) there was a secondary or tertiary diagnosis of affective disorder or schizophrenia. We were able to test this in the 1975 data and found that 13.7% (N=914) of the patients with "other" primary diagnoses who received ECT had secondary or tertiary diagnoses related to affective disorder. None had secondary or tertiary diagnoses of schizophrenia.

Sex, Race, and Age

About half of total admissions to the four types of psychiatric facilities in 1975 (N=514,394; 49.9%) and in 1980 (N=512,754; 47.7%) were women. Women, however, represented the great majority of ECT recipients: 41,126 (70.1%) in 1975 and 20,327 (64.5%) in 1980 (figure 1). The predominance of female over male ECT recipients was highly significant in 1975 ($Z=7.90$, $p<.0001$) but just barely significant in 1980 ($Z=3.11$, $p<.002$). The change in the percent of female ECT recipients over time was not significant ($Z=0.74$).

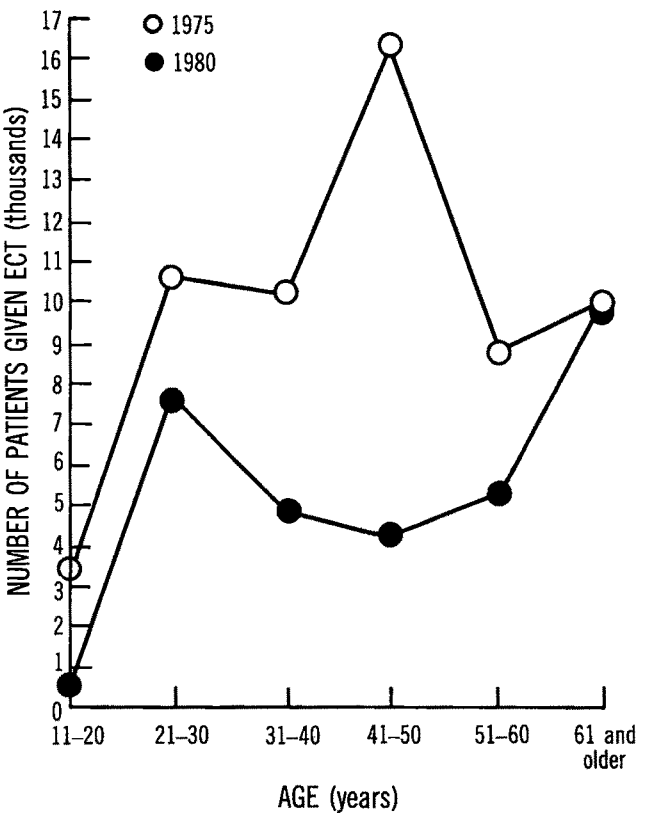
A predominance of women among ECT recipients was also seen in patients with affective disorder. Women accounted for 65.1% (N=213,373) of admissions with this diagnosis but 70.5% (N=30,115) of those

FIGURE 1. Use of ECT for Female Patients Admitted to or Discharged From Psychiatric Facilities in 1975 and 1980[a]



[a]Only admissions and discharges included in study, not resident patients.

FIGURE 2. Age of Patients Admitted to or Discharged From Psychiatric Facilities in 1975 and 1980[a]



[a]Only admissions and discharges included in study, not resident patients.

with this diagnosis given ECT in 1975; they were 61.7% (N=219,183) of admissions with affective disorder but 69.8% (N=15,349) of those with this diagnosis given ECT in 1980. The same was true of women with schizophrenia: they represented 47.5% (N=118,640) of total admissions with this diagnosis but 65.3% (N=6,074) of those with this diagnosis given ECT in 1975 and 43.0% (N=107,899) of admissions with this diagnosis but 50.6% (N=2,640) of those with this diagnosis given ECT in 1980.

Nonwhite admissions were much less likely to receive ECT than were white admissions, even when the number of admissions of whites and nonwhites was controlled for. In some types of facilities, almost no people of color received ECT—for example, the sample of state mental hospital patients in 1980 did not include a single nonwhite patient who received ECT.

The distribution of ECT recipients by age changed between 1975 and 1980 (figure 2). All age groups except that of patients 61 years old or older contributed to the overall 46% decrease in ECT use. The result is that a larger proportion of ECT recipients was 61 years old or older in 1980 than in 1975. (The proportion of patients within the 61 years old or older group who received ECT did not change over time.) The largest numerical decrease was in the 41–50-year-old group, while the group that was 61 years old or older was unchanged. The largest numerical decrease in each of the types of psychiatric facilities was seen in the 41–50-year-old group. The exception was the public general hospitals, in which there was no change in the 41–50-year-old group. In the public general hospitals, there were increases in all other age groups except the 11–20-year-old group, with the largest increase by far in the 21–30-year-old group.

In the four types of facilities taken together, the number of admissions with affective disorder who received ECT in the 21–30-year-old group increased as a proportion of the total group receiving ECT (figure 2). The increase in this age category consisted of a 230% increase in patients with affective disorder in public general hospitals and an 82% increase in patients with schizophrenia in private general hospitals.

To study the relative importance of gender, diagnosis, and age in receiving ECT, we performed a series of eight forward stepwise logistic regressions (one for each hospital type in 1975 and in 1980). In doing so, we were not attempting to build a complete predictive model, so full details of the models are not presented. In summary, the diagnosis of affective disorder was the most important predictor of ECT use, except in private psychiatric hospitals and private general hospitals in 1980, where age was most important and affective disorder was second most important. Affective disorder, age, and schizophrenia were more important predictors than sex in all instances except in state hospitals in 1980, where affective disorder was most important, followed by sex.

Patients were also studied with regard to whether

they had ever received any previous inpatient or outpatient care for mental disorder. We took this to be an indicator of whether ECT was being used as a first-line treatment. Patients who received ECT were not significantly more likely than those who did not to have received previous care in 1975 ($Z=2.14$) or in 1980 ($Z=1.72$). The percentage of patients given ECT who had received previous care did not change significantly between 1975 and 1980 ($Z=1.93$), although the percent of patients who did not receive ECT with previous care did increase over time ($Z=7.54$, $p<.0001$).

The legal status of patients (available only for 1980) showed that 1,580 (5.0%) of the patients given ECT were involuntarily hospitalized, compared with 306,792 (29.4%) of patients not given ECT who were involuntary. This pattern was seen in all four types of facilities.

DISCUSSION

In agreement with the literature as a whole, our study found that ECT use decreased markedly during the latter half of the 1970s. Although we could not examine the reasons for the decrease, two possibilities are regulatory pressure and the unwillingness of facilities to maintain the necessary staff and equipment for ECT. Another possible reason for decreased ECT use is the increased use of pharmacological agents, although our survey did not show an increase in the use of pharmacotherapy over the study period.

Also in agreement with the literature, we found that more women than men received ECT, although this difference disappeared when diagnosis (especially affective disorder) and age were controlled for.

Our data bear out the findings of Morrissey et al. (7) and Babigian and Guttmacher (8), who indicated that ECT is primarily used for white middle- or upper-class patients with third party coverage. What is not clear is whether the underuse in minority and other disadvantaged groups appropriately reflects differential therapeutic needs of these groups or ECT is inappropriately being denied to these patients for some reason.

Our results did not show ECT as being a second line treatment more in 1980 than in 1975. However, our index of this was a rough one, and this question deserves more attention in future research.

The 1976 APA study (11) warrants special discussion because it is widely quoted (5, 13) and because our study showed many fewer patients receiving ECT in 1975. (The NIMH and APA studies were done during almost the same time period.)

There are some important methodological differences between the two studies. The APA study was a survey of practitioners (a sample of APA members), while ours was a survey of patients in facilities. The APA survey was based on a 6-month recall period, and the NIMH survey was based on medical records. There may have been some inaccuracy of memory among practitioners in the APA study, but it is not clear whether the physicians responding to the APA survey would have tended to underreport or overreport. One bias toward overreporting could have resulted from asking how many patients the respondent personally treated and also how many patients were recommended for ECT to psychiatric residents under the respondent's supervision. Potentially, such patients could have been counted twice. In our study there could have been some cases in which a record of ECT treatment in the chart may have been missed. Also, VA hospitals and multiservice general hospitals were not surveyed by NIMH in 1975, and office-based practices were not surveyed at all. All of these effects, although perhaps small in and of themselves, could bias the NIMH data toward lower figures.

Still, a large discrepancy exists between the two studies. In this regard, it is important to note that the APA sample was inflated to the entire population of psychiatrists with an assumption that nonrespondents to the survey (25% of the sample) used ECT in the same amounts as did the respondents. One could argue that because ECT is a controversial treatment—one that engenders strong advocacy among those who use the treatment and negative feelings among many of those who do not—respondents to the APA survey were very likely to be ECT users and nonrespondents much less likely to use ECT. Those who did use ECT would have had a vested interest in responding to the survey (knowing that it would very likely be used to support the use of ECT), and those who opposed the use of ECT would not be inclined to respond. If we make these assumptions and recalculate the APA data, we come up with a figure of 66,520 patients receiving ECT over the survey year. This is much closer to the 58,667 reported in the NIMH data, although the APA figure is still clearly higher.

CONCLUSIONS

In agreement with most of the literature, our data indicate that the use of ECT is decreasing. It is by no means disappearing, however, and in public general hospitals its use was at least as prevalent in 1980 as it was in 1975. Why the latter should be the case is an important question for future studies. Women receive more ECT than men, but age and diagnosis are much more important than being female. Also in accord with the existing literature, we find that ECT is largely used as a treatment for patients who are white, voluntary, and paying their way in private institutions.

Important research questions on use of services yet to be answered are the details concerning referral for ECT—who refers patients for ECT and why; perceptions as to appropriate indications for ECT, such as are found in a recent article by Bland and Brintnell (22); and how ECT fits into the overall course of treatment.

Still another avenue of inquiry regarding ECT is what has happened since 1980. Is ECT use going back up, as some anecdotal reports and at least one state

report (23) indicate? Will an emphasis on shortened lengths of stay lead to increased ECT use as a first line treatment? In approaching these questions, we feel, along with Morrissey et al. (7), that it is important for informed action and health policy formulation to be based on empirical, not ideological, criteria. As a part of the development of these empirical criteria, research questions on use of services such as those addressed in this paper are at least as important as research on the clinical use of ECT.

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Relationship Between Russian Roulette Deaths and Risk-Taking Behavior: A Controlled Study

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A review of medical examiner records yielded data on 19 men and one woman who died playing Russian roulette. The men differed significantly from 95 male suicide victims who died of gunshot wounds to the head on several variables including age, race, ethnicity, religion, citizenship, marital status, living situation, health, and the likelihood of the death being witnessed. The Russian roulette victims were significantly less likely to die in the bedroom, die in the morning, leave a suicide note, and be depressed but were significantly more likely to have alcohol or drugs in their body fluids and to have a previous history of drug and alcohol abuse.

(Am J Psychiatry 1987; 144:563–567)

Russian roulette is a "deadly game of chance in which a person spins the cylinder of a revolver holding only one bullet, aims the gun at his head, and pulls the trigger" (*Webster's New World Dictionary*, 1982). The "roulette" element of the phrase comes from the well-known gambling game in which a small metal ball is spun onto a revolving wheel, stopping in one of the 38 numbered compartments. The "Russian" part of the phrase may have originated from a popular mess pastime played by officers of the Czar's army or may be of much more recent origin, traced to the presumed fatalism of Russians generally (1).

The earliest form of Russian roulette was described in the first major prose novel of Russian literature, *A Hero of Our Time* (2). In this novel, in a chapter called "The Fatalist," the hero Pechorin tells the story of Lieutenant Vulich, who is courageous and a risk taker and has only one passion: gambling. Vulich, to settle an argument between the other officers on predestination, bets on himself. He tests his fate and takes the ultimate gamble and risk by discharging a pistol at his temple with the hope that the gun had not been loaded. He wins but later is a victim of his fate and is killed. Pechorin, in turn, as if infected by Vulich's risk-taking behavior, tests his fate, gambles with death in another way, and wins. This great classic story demonstrates a number of interesting themes surrounding Russian roulette: its identification as the ultimate game of chance, the gamble with death, the testing of fate (fatalistic aspect), the identification of it as an act of bravado, and the demonstration of an extreme form of risk-taking behavior.

Baechler (3) defined risk taking as any dangerous activity in which there is a chance of loss of life (e.g., automobile racing, mountain climbing). He pointed out that all risk-taking behavior could reflect suicidal tendencies. Weiss first noted that gambling with death and risk-taking behavior, as seen in Russian roulette, are inherent in many suicide attempts (4). Suicide attempts are consciously or unconsciously arranged in such a manner that the outcome may vary from almost certain survival to almost certain death; and "fate"—or at least some force external to the conscious choice of the person—is compelled in some magical way to make the final decision (4). Baechler (3) divided all suicides, by the degree of risk-taking behavior displayed, into intended and ventured. In intended suicides, the subject uses a method that, except for extreme luck, must lead to death. Baechler placed Russian roulette under ventured suicide, which encompasses all conduct in which there is a very high probability of death, i.e., there is a gamble with death.

In order to better define the relationship between Russian roulette deaths and intended suicides, we compared a group of subjects who died playing Russian roulette to a group of suicide victims who died of gunshot wounds to the head that were not inflicted during Russian roulette. These suicide victims were chosen as a control group because theoretically the suicide was intentional, with little or no risk taking (3, 5), and involved a physical mechanism similar to that of Russian roulette. To our knowledge this is the first controlled study of Russian roulette deaths, which have not been studied in detail before.

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The authors thank Rubens King-Shaw, Jr., Robin Cohen, and Roe Roberts for assisting with data analysis; Ms. Collen Aldrich for manuscript assistance; Orlando Santana for assisting with data collection; and Ms. Carla Crystal Rose Watson for manuscript typing.

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METHOD

Russian roulette victims were identified through review of the case files for 1957–1985 of the Dade County, Fla., medical examiner, who had differentiated them through research in accordance with established principles of medicolegal investigation (6). Of 6,534 suicides consecutively recorded in the medical examiner's office during the 27 years studied, 20 Russian roulette victims (19 men, one woman) were identified, representing 0.31% of the total. The men represented 0.44% of all male suicide victims and 0.89% of all such victims who used firearms. The one woman represented 0.04% of all female suicide victims and 0.18% of all such victims who used firearms.

For each male Russian roulette victim, we randomly selected (7) from the same year (to control for the changing demography of Dade County), as a control group, five male suicide victims who had died from gunshot wounds to the head. Age matching was considered but was not done, since it was known that this variable was important in risk-taking behavior. The 5:1 matching of control subjects to Russian roulette victims provided a Pittman's efficiency value of 1.67 compared to a unitary value from 1:1 matching (7).

All available information on the charts of Russian roulette victims and the charts of the control group was analyzed and coded on a standardized instrument (available on request) that was specifically developed for that purpose. The charts of the cases selected usually contained the following information: death certificate, report of the police officer investigating the death, medical examiner's autopsy report, toxicology report, suicide note if any, newspaper clippings, hospital records if the patient lived for a while, and previous hospital records if available. The items of the coding instrument were developed to reflect standard, reliable, and routinely reported information of various professionals investigating the death. Because of the number of professional reports reviewed and the fact that most of the information sought was required for the record, the frequency of missing data for objective variables (e.g., age) was extremely small (approximately 1%–5%). Missing data were coded as unknown, and all calculations for those variables were done with the remaining data. This approach may have decreased the numbers of subjects for some variables, causing nonsignificant results. The objective nature of the variables examined and the professional source of the data make it unlikely that any significant amount of the data was unreliable.

Nonobjective variables, e.g., recent history of senility or confusion and recent history of depression, were usually identified from the police report or the medical examiner's report. If there was any mention of these variables, the coding instrument was marked positive for the variable; e.g., if there was any mention of "despondent recently" as described by relatives, the coding instrument was marked positive for the variable of recent history of depression. Because both the witness to the Russian roulette or suicide and the investigating professional interpreted this information, it is likely that a much greater percentage of information for nonobjective variables was unreliable.

TABLE 1. Significant Differences Between Men Who Died During Russian Roulette and Men Who Committed Suicide With Firearms

Variable	Death by Russian Roulette (N=19) N	%	Firearm Suicide (N=95) N	%	χ^2 (df=1)	p
Age-related variables						
Single	10	52.6	12	12.6	13.80	<.005
Living with spouse or child and spouse	6	31.5	58	61.0	6.85	<.01
Living with someone of opposite sex (not a family member)	5	26.3	1	1.0	15.52	<.005
Student	6	31.5	3	3.2	13.90	<.005
Health good or very good	18	94.7	46	48.4	11.98	<.005
Other demographic variables						
Black	6	31.5	3	3.2	13.90	<.005
Latin	10	52.6	16	16.8	9.58	<.005
Not a U.S. citizen	7	36.8	10	10.5	6.69	<.01
Catholic	9	47.3	12	12.6	10.51	<.005
Isolation variables						
People in area at time of death	19	100.0	45	47.3	14.89	<.005
Discovered by friend	11	57.8	12	12.6	17.43	<.005
Discovery expected	19	100.0	11	11.6	57.53	<.001
Last seen by a friend	11	57.8	9	9.5	22.42	<.001
Depression variables						
Death in bedroom	4	21.0	7	49.8	6.39	<.05
Death in morning	4	21.1	44	46.3	5.25	<.05
Suicide note found	0	0	28	29.5	7.98	<.01
Recent history of depression	9	47.3	75	78.9	7.72	<.01
Alcohol/drug variables						
Alcohol and/or drugs in body fluids	11	57.8	28	29.5	4.49	<.05
Psychiatric history of alcohol and drug abuse	11	57.8	24	25.3	6.46	<.05

Through chi-square analysis (7), the tabulated data were analyzed for differences between the Russian roulette victims and control subjects. Because there were no other data hypotheses besides age, and because this was an exploratory study with some missing data, multivariate analysis was not performed. All chi-square tests with a p value >.01 were interpreted with caution.

RESULTS

The mean±SD age of the 20 Russian roulette victims was 27.7±1.85 years, compared with 50.8±16.05 years for the 95 control subjects ($t=10.56$, $df=51$, $p<.001$). The male Russian roulette victims differed significantly from the control subjects in race, ethnicity, marital status, living situation, and several other variables (see table 1). There were no

significant differences between the two groups with respect to the following variables: recent history of loss, life problems, and hostility and belligerence; previous psychiatric history (all of the following: alcohol abuse, drug abuse, and suicide attempts) and history of psychosis; type of residence; birthplace (Cuba); family in Miami (no); living with family; type of family (spouse only); living alone or with parents; employed full-time; employed in a semiskilled or skilled job; place of death (home, friend's home, the street); people present in area at time of death (spouse or lover or other family members); dead on discovery; area of death (living room or kitchen); how dressed (fully); date of death (August or September and December or January); death on weekend or Friday night; in armed forces (yes); and record of felonies or misdemeanors.

Of the male Russian roulette victims, 57.8% (N=11) fired more than once, 26.3% (N=5) had played the game before, and 15.7% (N=3) loaded more than one bullet into the gun. All of the Russian roulette victims died in the presence of others. The "others" broke into the following groups: male and/or female friends, 42.1% (N=8); girlfriends, 26.4% (N=5); and family members, 31.5% (N=6). A total of 68.4% (N=14) of all the Russian roulette deaths were witnessed by female others: 100% of the girlfriend (N=5) and family (N=6) groups were made up of female others, while 37.5% (N=3) of the friend group contained a female other. In 73.6% (N=14) of the cases these others were advised by the Russian roulette victim that they would now be shown a game they could play, and 10.5% (N=2) of the others actually participated.

DISCUSSION

Our findings on age and age-related variables indicate that being young is an important predisposition to playing Russian roulette. These findings are supported by experimental studies indicating that risk-taking behavior decreases with age (8).

Data from our study show that men are much more likely than women to die from playing Russian roulette. In addition, even when the greater tendency of men to commit suicide by firearms is taken into account, women are less likely to die by Russian roulette. Experimentally, women are less prone to risk-taking behavior (8). Our other demographic variables may be interrelated, since a significant percentage of the large Miami Latin community is black, Roman Catholic, and probably not yet of U.S. citizenship. To our knowledge, none of these demographic variables has been linked to risk-taking behavior. These findings indicate that the Miami Russian roulette victim may have a unique ethnic profile.

One would expect Russian roulette to be a nonsolitary pursuit. Variables indicative of isolation appear to support the idea that while firearm suicides occur when the victim is geographically isolated from people, this is not true of Russian roulette deaths.

To Baechler (3), the game of Russian roulette is an extreme form of risk-taking behavior. Suicide attempts are also characterized by risk-taking behavior (8, 9), and subjects who attempt suicide have been found to take more risks on experimental risk-taking procedures than matched control subjects (9). Other literature (10) also indicates that recklessness or risk-taking behavior may have an antidepressant effect in depressed young males. Thus it is possible that the Russian roulette victims in our study were depressed and were trying to treat their depression through risk-taking behavior. A number of variables previously associated with depression, e.g., death in the bedroom (table 1), may reflect the wish to die, which is reflected in the wish to sleep and never wake up (11). Death in the early morning may reflect the propensity of the suicide victim to have a sleep disturbance as a consequence of being depressed (11). Close examination of these depression variables reveals that they both support and refute the idea that Russian roulette victims were depressed. However, we are impressed by the frequency of these variables in the Russian roulette victims. In addition, we believe that the way in which victims chose to play Russian roulette (firing more than once, playing more than once, and loading more than one bullet) exposes a strong wish to die that is suggestive of a severe depressive component.

Some authors (12) believe that the adolescent glorification of risk-taking behavior (e.g., daredevil acts and fighting) is due in part to the adolescent need to attain status through the demonstration of competence at personal physical risk. Because of this need the male adolescent, although dreading death like the female, reacts to the fear of death as a deplorable, cowardly trait (13). Thus, in a suicidal male adolescent, a fear-versus-shame conflict is activated, as a result of which he is more apt to commit suicide in order to avoid the self-accusation of cowardice (13). This male adolescent need may lead to the common male experience called the "ordeal" (3). Baechler (3) has defined the ordeal as a situation in which one risks one's life in order to prove oneself to oneself or to solicit the judgment of others. In an ordeal, the usual stake is the subject's value. In it he tries to prove his courage, ability to master his fear, and ability to master his environment, thereby winning his reward. The ordeal is a test directed not only at the subject but also at his friends, family, and community.

Baechler (3) believes that in the ordeal, it is not the subject but the others who play the principal role. This concept is supported by the experimental demonstration of the importance of others in determining risk-taking behavior: subjects with low esteem take greater risks than subjects with high esteem in the presence of an audience (14); decisions reached by individuals on risk-taking behavior are more cautious than those reached by a group (risk shift) (15); in a group, subordinate observers advocate higher risks than

leader negotiators (15); and risk shift phenomena occur even in groups where subjects do not reveal their preferred risk levels (16). In support of these concepts, our findings point to the importance of the presence of others—the peer group other and the female other—in Russian roulette. Therefore, if the young mean age of the Russian roulette victims is taken into account, the concepts of the adolescent struggle to demonstrate competence at personal physical risk and of the ordeal may apply to Russian roulette deaths. The presence of others could serve not as a deterrent to Russian roulette victims but as a stimulus to their risk-taking behavior.

Baechler (3) identified Russian roulette as a game of chance in which winning is the result of fate alone and the capriciousness of chance constitutes the unique appeal of the game. If winning were constantly assured, there would be no passion in the game. In addition, the greater the possible loss, the greater the fascination with the game. Because the supreme loss is life, the most exciting game imaginable is where each player gambles with his or her life, submitting himself or herself to chance alone. Russian roulette is such a game (3). Gambling is a contrived form of risk taking in a controlled setting, and risk taking may be one of the major attractions for ordinary gambling. Experimentally, it has been determined that a relationship exists between risk taking and gambling: risk takers, as defined by their willingness to approach risks, were rated by others as risky, being optimistic about outcomes, and preferring to gamble (17). A relationship may also exist between depression and the wish to gamble. Niederland (18) reported that political exiles who had seldom or never gambled did so in response to recurrent depressions, which were relieved by the gambling. Other authors (19) have noted that compulsive gamblers may begin their gambling after a major life crisis or major stress.

Psychodynamically, gambling may attract by allowing individuals to indulge in the human illusion of omnipotent control over destiny (18). Thus, gambling is a magical attempt to compel fate to do its duty, to reverse its course, and to regain the feeling of omnipotence and grandeur by winning (18). To feel powerful, one needs to feel omnipotent. It is therefore interesting that individuals high in power needs have to be in the limelight and may do so in gambling situations by taking more extreme risks (20). From this viewpoint, the key probability for them is not winning but being noticed and admired for being a "big gambler" (20). We believe, as our results indicate, that a large percentage of Russian roulette victims do look on Russian roulette as a game they can play.

Drinking alcoholic beverages may increase risk-taking behavior. Thus when the risk-taking behavior of sober subjects was compared to that of alcohol-intoxicated subjects, it was found that intoxicated subjects accepted greater subjective risk (21). In addition, it appears that high risk-taking behavior scores may be related to a history of high use of multiple drugs (22) and alcohol (23). Our findings regarding alcohol and drug use support these experimental findings. One wonders if this form of risk-taking behavior (Russian roulette) would have occurred without drug or alcohol ingestion.

What are the implications of this study for clinical psychiatric practice? A major implication is that if one considers Russian roulette a form of suicidal behavior, suicides by this method are extremely rare. It is therefore likely that the vast majority of psychiatrists will not encounter this form of risk-taking behavior. However, if a patient or his or her significant other gives a history of this behavior, that patient could be a young, nonwhite, Latin, Catholic, single male of recent arrival in the United States. Conversely, if a patient with this profile is psychiatrically examined after a firearm suicide attempt, the examiner should inquire about recent forms of risk-taking behavior including Russian roulette. Because of the involvement of the female other and peer group members in Russian roulette deaths, these inquiries should also be directed at these individuals. In addition, because a high percentage of Russian roulette victims act in ways that ensure their death, identified potential victims should be considered at high risk for suicide or death by Russian roulette. These potential Russian roulette victims should be carefully examined for the presence of drug or alcohol abuse, depression, and conscious suicidal ideation; history of recent loss, drug or alcohol abuse, suicide attempts, risk-taking behavior including Russian roulette, and risk-taking behavior during times of stress or depression; and a fascination with the game aspects of risk-taking behavior including Russian roulette and with the gamble with death. In terms of treatment, it may be profitable to point out to the patient the relationship between his risk-taking behavior and stress, drugs, alcohol, and depression. The significant other may need to be made aware of her role as a possible stimulus to the subject's risk-taking behavior. Psychiatrically, one should never forget that extreme forms of risk-taking behavior may reflect depression associated with suicidal potential.

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Sources of Conflict in the Medical Marriage

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The authors surveyed a sample of 134 physicians and 125 physicians' spouses regarding marital satisfaction, sources of marital conflict, and complaints about their spouses. Contrary to conventional wisdom, the number of hours at work did not relate to the degree of marital satisfaction. The chief sources of conflict in the medical marriage appear to revolve around differences in the partners' needs for intimacy, perceptions of the problems in the marital relationship and in each other, and communication styles. Lack of time due to the demands of practice seems to be a complaint that serves the function of externalizing the conflicts in the marriage onto factors outside the marriage.

(Am J Psychiatry 1987; 144:567–572)

Studies of medical marriages suggest that in many cases both marital partners lead what Thoreau termed "lives of quiet desperation." While many physicians and spouses report unhappy marriages (1, 2), they tend to stay in their marriages rather than to divorce and look for new partners (3, 4). In their elegant prospective study of 47 physicians and 79 matched control subjects, Vaillant et al. (1) found that almost half had experienced unhappy marriages even though the sample was skewed in the direction of health. What is less clear are the underlying factors that contribute to conflict and unhappiness in the physician's marriage. By far the most common source of conflict cited in the literature is the physician's tendency to work long hours, leaving little time for interaction with his or her spouse (2, 5–12). Despite the popularity of this explanation, studies have failed to find any correlation between long hours of work and either poor marriage or divorce (1, 3).

The time the physician spends at work and the lack of time he or she spends at home may well be effects, rather than causes. Working long hours may be a symptom of an underlying characterological compulsiveness in the physician (11, 13–15) or may reflect marital problems in an unhappy relationship that the physician wishes to avoid (1, 5, 8, 16). Tension in the medical marriage may be related to clashes of character style between the compulsive workaholic physician and the dependent spouse with an inordinate need for affection and nurturing (5, 17). The physician may avoid open conflict brought on by the neediness of the spouse by prescribing medications for him or her or by

Received April 21, 1986; revised Sept. 26, 1986; accepted Nov. 3, 1986. From the Menninger Foundation. Address reprint requests to Dr. Gabbard, the Menninger Foundation, Box 829, Topeka, KS 66601.
Funded by the Menninger Foundation.
The authors acknowledge the contributions of Mr. Brent Menninger and Mr. Chris Beasley.
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spending more time at the office (1, 3). In the traditional marriage of male physician and female nonphysician spouse, marital tension may arise from the woman's feeling that her identity is contingent on her husband's (18) and from the failure to clarify role differentiation in the marriage (19, 20). Finally, an unhappy marriage may simply be an adult derivative of the physician's emotionally barren family situation as a child (1).

The acceptance at face value of lack of time for one's spouse and family as the chief source of marital conflict seems both inadequate and oversimplified. A more thorough understanding of marital unhappiness in the medical marriage is needed if we physicians are to minimize the suffering so prevalent in ourselves, our colleagues, and our families. This report is intended to further our understanding of the factors that contribute to discord in the physician's marriage.

METHOD

For the last 10 years, the Menninger Foundation has sponsored a 5-day continuing education workshop for physicians and their families at Estes Park, Colo. The 240 physician couples who have participated in these workshops served as the data base for the present study. We devised a questionnaire for both physician and spouse to obtain information about the demographics, psychological health, work patterns, marital gratification, and perceived sources of marital conflict from each. During the summer of 1985, these physician couples were sent questionnaires accompanied by an informed consent document and a cover letter assuring confidentiality. The signed informed consent was sent to the chairperson of the Menninger Foundation Ethical Review Committee, while the coded questionnaire was sent to the researchers, thereby eliminating the possibility of matching names with questionnaires.

In addition to a simple 5-point rating scale of marriage gratification, both the physician and the spouse questionnaires listed 15 potential sources of conflict in the marital relationship. The respondent was asked to rate these issues on a scale of 0 to 5 according to their importance as a source of conflict in his or her marriage (0="not applicable," 1="of limited importance," 2="of mild importance," 3="of moderate importance," 4="of considerable importance," 5="of paramount importance"). Both physician and spouse were also asked to rate 12 frequently heard complaints about one's spouse according to their importance and applicability as a problem in their particular partner. A similar 0–5 rating scale was used.

RESULTS

After a second mailing, 134 of the 240 physician questionnaires were returned, for a return rate of 55.8%. A total of 125 of the 240 spouse questionnaires were returned, constituting a 52.1% return rate. Of these physicians, 93.3% (N=125) were male, while 97.6% (N=122) of the spouses who returned questionnaires were female. There were 111 marital couples in which *both* physician and spouse had completed a questionnaire. Of this group, 106 of the couples were composed of a male physician and female nonphysician spouse, two couples were composed of a female physician and a male nonphysician spouse, and three couples were dual-physician marriages.

The mean age of the physician respondents was 44.6 years, while that of the spouse respondents was 42.7 years. The overwhelming majority of both physician and spouse groups were white (94.8% [N=127] and 96.8% [N=121], respectively). For 90.3% (N=121) of the physicians and 91.2% (N=114) of the spouses, the current marriage was their first. Although physicians from both rural and metropolitan areas responded to the survey, our sample was skewed toward the rural or small-town practitioner. Some 50.7% (N=68) came from cities of less than 50,000 population, while only 13.4% (N=18) lived in population centers of greater than 500,000. Of those in the spouse group, 84.8% (N=106) had at least a college degree, and 60.0% (N=75) were employed outside the home.

Our physician group was almost equally divided between primary care practitioners (55.2%, N=74) and specialists (44.8%, N=60). Our sample consisted largely of front-line practitioners. Only 5.2% (N=7) listed an academic setting as their primary practice situation; 28.4% (N=38) were in solo practice, 24.6% (N=33) in a single specialty group, and 29.1% (N=39) in a multispecialty group. Of the 120 physicians who worked full-time, 56.4 hours per week constituted the mean workload in the typical week.

Mental Health and Marital Satisfaction

Similar to the sample of Vaillant et al. (1), our sample of physicians and spouses appeared to be skewed in the direction of psychological health. Only 3.7% (N=5) of the physicians had a history of inpatient psychiatric treatment, 2.2% (N=3) had received treatment for alcoholism, and a similar number (N=3) had received treatment for drug abuse. Figures for the spouse sample were similar. Of the physicians, 24.6% (N=33) had received psychiatric outpatient treatment, while 20.8% (N=26) of the spouses had visited a psychiatrist as an outpatient.

Given the apparent health of the population, it was surprising to note that 47.0% (N=63) of the physicians and 48.0% (N=60) of the spouses reported having sought marital counseling. (Our figure of 47.0% is identical to the percentage of unhappy marriages in the sample of Vaillant et al. [1].) An additional 28 physicians (21%) and 21 spouses (17%) had seriously considered it. Hence, some 68% (N=91) of our sample of physicians and 65% (N=81) of the

TABLE 1. Rating of Marriage Gratification by Physicians and Their Spouses

Rating of Marriage Gratification	Physicians (N=134)		Spouses (N=125)	
	N	%	N	%
1-extremely gratifying	44	32.8	36	28.8
2-moderately gratifying	61	45.5	51	40.8
3-mixed	15	11.2	24	19.2
4-moderately nongratifying	11	8.2	6	4.8
5-extremely nongratifying	1	0.7	6	4.8
No rating	2	1.5	2	1.6

spouse sample had either sought or considered marital counseling.

Given that approximately two-thirds of both physicians and spouses had either sought or considered marital counseling, the data from the questionnaire concerning marital gratification are puzzling. Table 1 reflects the fact that the preponderance of our subjects found their marriages either extremely or moderately gratifying. How are we to understand this apparent discrepancy between the need for marital counseling and such high levels of marital gratification?

One explanation is that the respondents were more gratified in their marriages as a result of counseling. Further analysis of the data, however, suggests that this is not the case. Using the Newman-Keuls test for comparison of pairs of means, following a significant overall F test, we found that the data clearly indicated that those physicians who had never considered marital counseling were significantly more gratified in their marriages (mean rating=1.48) than those physicians who had sought marital counseling (mean=2.31) or those physicians who had only considered marital counseling (mean=2.09) ($df=127$, $p<.01$ in both comparisons). There was no significant difference in marriage gratification between those who had sought marital counseling and those who had only considered it. The same levels of significance were found in similar comparisons of the spouse groups. These findings argue against the notion that counseling contributed to higher levels of marriage gratification in this series.

Other possible explanations of the discrepancy are that couples with significant marital problems may refer to their marriage as either moderately or extremely gratifying simply because of lowered expectations regarding connubial bliss or because of a need to project a facade of marital harmony. The former explanation is further supported by the observation that 48 respondents, many of whom had rated their marriages as gratifying, appended written comments to the questionnaire describing a variety of marital difficulties. Only 29.1% (N=39) of the physicians had considered separating or divorcing, while 38.4% (N=48) of the spouses had given serious thought to leaving the marriage. Given the preceding figures regarding serious marital counseling, these percentages are lower than one might expect. This observation lends support to the notion that the partners in medical marriages may tolerate considerable despair without deciding to divorce.

Perceptions of Sources of Conflict

Table 2 illustrates the ranking of sources of conflict in the marital relationship by the entire sample of physicians and by the entire sample of spouses according to the mean rating on the 0–5 scale described earlier. While concerns about "lack of time for fun, family, and self" ranked first in the lists of both physician and spouse, there was a noteworthy discrepancy in the perception of "amount of time away from home at work" as a source of conflict, with the physicians tending to see it as a much greater source of conflict than the spouses. The other noteworthy discrepancy in the two lists was a tendency of the spouse group to consider "lack of intimacy" as a much greater source of conflict than the physician group. Apart from these two items, the two groups ranked sources of conflict fairly similarly.

Since these data apply to all physicians and spouses who responded to the questionnaire survey, it is difficult to assess whether individual couples differed in their perception of problems in their own relationship. Many individual differences could be buried in mean figures of the entire group. Using a Pearson product moment correlation, we took a closer look at a more restricted segment of our sample: the 111 married couples who had sent in completed questionnaires. In particular, we looked for response discrepancies between members of individual marital couples. Table 2 demonstrates that this analysis revealed significant but small correlations, indicating little overlap in variance. If this analysis is viewed as similar to a reliability test, one can readily see that on no item among the entire list of 15 did husband and wife approach the 0.7 or 0.8 figures that are considered acceptable levels of reliability, indicating about 50% shared variance. This finding may be understood to suggest that individual husbands and wives tended to rate the importance of items differently rather than agreeing on their sources of conflict. Listed in order from the most discrepant to the least discrepant, they were as follows: 1) tension in the home, 2) quality of sexual relations, 3) finances, 4) lack of intimacy, and 5) religious differences. Hence, while individual physicians and spouses did not tend to rate any of the sources of conflict similarly, these were the five areas around which there was the most disagreement.

On both questionnaires we asked the physician and spouse to rate on a 0–5 scale the importance of various problems in their marital partners. Table 3 shows the rank order of these problems by the entire sample of physicians and by the entire sample of spouses. A cursory glance at these findings reveals major discrepancies regarding which problems were perceived as important to which marital partner. The major concern of physicians was that the spouses were not interested in having sexual relations, while the primary

TABLE 2. Sources of Conflict Cited by Physicians and Their Spouses

Source of Conflict	Rank Order: Physicians (N=134)	Rank Order: Spouses (N=125)	r[a]	df	p
Lack of time for fun, family, and self	1	1	0.417	83	<.001
Amount of time away from home at work	2	8	0.441	86	<.001
Frequency of sexual relations	3	4	0.481	82	<.001
Finances	4	5	0.291	83	<.01
Money management	5	3	0.458	82	<.001
Tension in the home	6	7	0.279	85	<.01
Lack of intimacy	7	2	0.296	80	<.01
Lack of shared responsibilities for children and for work around the house	8	6	0.438	81	<.001
Philosophy of child rearing	9	9	0.445	84	<.001
Quality of sexual relations	10	10	0.287	81	<.01
In-laws	11	11	0.397	84	<.001
Family size	12	15	0.533	85	<.001
Jealousy	13	13	0.424	82	<.001
Religious differences	14	14	0.341	81	<.01
Taboo subjects	15	12	0.466	84	<.001

[a]Pearson product moment correlations are based on the 111 married couples who sent in completed questionnaires.

TABLE 3. Importance of Problems Perceived in Spouse by Physicians and Their Spouses

Problem Perceived in Spouse	Rank Order: Physicians' Perception (N=134)	Rank Order: Spouses' Perception (N=125)	r[a]	df	p
Is not interested in sexual activity	1	9	−0.140	104	n.s.
Doesn't empathize with my role and position	2	4	0.258	104	<.01
Doesn't listen to me	3	3	0.110	104	n.s.
Expects too much work around the house from me	4	8	0.255	104	<.05
Complains too much	5	7	0.032	104	n.s.
Doesn't provide enough emotional support for me	6	2	0.377	104	<.001
Nags me too much about my lack of time at home	7	10	0.038	104	n.s.
Doesn't talk to me enough	8	1	0.240	103	<.05
Doesn't respect me enough	9	5	0.406	103	<.001
Expects too much from me sexually	10	6	−0.205	104	<.05
Jealousy	11	11	0.264	104	<.01
Pays more attention to other members of the opposite sex than to me	12	12	0.138	104	n.s.

[a]Pearson product moment correlations are based on the 111 married couples who sent in completed questionnaires.

complaint of spouses was that the physicians would not talk to them. The high ranking of "doesn't listen to me" by the physicians implies that one of the reasons the physicians did not talk to their spouses as much as their spouses would like is that the physicians did not feel that their spouses were listening to them.

Since these rankings reflect the ratings of *all* the physicians and spouses in the sample, we again risk burying the individual differences in group means. Hence, we applied Pearson product moment correlation analysis to the 111 couples in which both completed the questionnaires to determine the extent to which partners of the marital dyads agreed in their views of the major problems of one another. Table 3 suggests that the responses of individual marital partners were even more discrepant than their responses about the sources of conflict in the relationship. Two items, both dealing with sexuality, were even negatively correlated: "Expects too much from me sexually," for example, was given a 5 rating by six spouses and a 4 rating by six spouses, while no physicians rated it either 4 or 5. Similarly, "is not interested in sexual activity" was rated as "not a problem" by 60 spouses, but only 26 physicians rated it that way. Other problems that were most discrepantly perceived were as follows, listed in order from the most to least discrepant: 1) complains too much, 2) nags me too much about my lack of time at home, 3) doesn't listen to me, and 4) pays more attention to other members of the opposite sex than to me.

Tension, Time, and Absence From Home

To investigate further whether the number of hours away from home at work was truly the major source of tension in the medical marriage, we employed univariate independent group t tests to compare those physicians who worked more than 60 hours per week with those who worked 40–50 hours per week. (Because of varying Ns, multivariate analyses were not possible. To guard against chance results, only consistent patterns of findings are reported here.) While the physi-

cians in the group that worked more hours tended to rate "lack of time for fun, family, and self" as a significantly greater source of tension than those in the group that worked fewer hours (mean=3.61 versus 2.96; t=2.50; df=93, p<.02), there was no significant difference in the level of marriage gratification between the two groups. Similarly, there were no significant differences in the responses of the spouses of these two groups of physicians.

In an effort to identify other factors that might contribute to greater marital gratification, we compared the group of physicians who had never considered or sought marital counseling (N=43) with those who had sought or considered it (N=91). Analysis of variance revealed a significant relationship between time spent talking to one's spouse and whether or not marital counseling had been considered or used. Among the physicians, the group that had sought marital counseling averaged 30.5 minutes per day talking with their spouses; the group that had considered marital counseling averaged 37.8 minutes per day; and the group that had neither considered nor used marital counseling averaged 57.3 minutes per day (df=126, p<.001). Among the spouses, the group that had sought marital counseling reported talking 41.6 minutes per day; the group that had considered marital counseling reported 42.7 minutes per day; and the group that had neither considered nor used marital counseling reported 61.0 minutes per day (df=121; p<.05). Whether there is a cause-and-effect relationship cannot be concluded from these data, but the findings are certainly consistent with the notion that couples who communicate more have less need for marital counseling.

DISCUSSION

The findings of this study must be interpreted cautiously. First of all, since the vast majority of our sample consisted of traditional marriages of a male physician and a female nonphysician spouse, our results cannot be readily generalized to dual-physician marriages or to those characterized by a female physician and a male nonphysician spouse. A second limitation of our study is that our sample was self-selected in the sense that only physician couples who came to a seminar for physicians and their families participated in the study. We cannot, therefore, assert that these findings apply to all couples in which the man is a physician. However, for the most part, the workshop has not drawn disturbed couples in search of marital therapy. On the contrary, our data suggest that the participants tend to be psychologically healthy. The strikingly low prevalence of impairment may well reflect the fact that physicians who are willing to explore their marriages are different from those who are not. The workshop is described as a continuing education seminar, *not* as a treatment experience.

We cannot, of course, claim that the sources of conflict that we have identified are unique to the marriages of physicians. Our intent was not to differentiate the marital problems of physicians from those of a control group of other professionals. Rather, given that the high proportion of poor medical marriages has been compellingly demonstrated by an elegant prospective study (1), our goal was to examine a group of physician marriages in some detail to understand better the sources of that discord. A unique feature of our study is the examination of a reasonably large sample of physician couples in which *both* members were surveyed and in which the physician was a nonacademic practitioner. The generalizability of previous studies has been limited because of a tendency to concentrate on academic settings and to focus on either physician or spouse, but not on both.

Within the limitations of our data, several findings deserve further comment. Our results suggest that the physician's complaint of insufficient time to attend to the needs of his or her spouse appears to be more an excuse for marital discord than an explanation. Our findings confirm those of other investigators (1, 3)—i.e., that there is *no* relationship between working longer hours and turmoil in the medical marriage. There also appears to be some discrepancy in the perception of lack of time as a problem. The physicians as a group ranked "time away from home" as the second most important source of conflict in their marriages, while the spouses ranked the same dimension eighth in importance. For the physician, lack of time due to the demands of practice seems to be a complaint that serves the function of externalizing the conflicts *in* the marriage onto factors *outside* the marriage.

Lack of time does not appear to be the chief source of conflict in the medical marriage, conventional wisdom notwithstanding. The marital partners seemed to have differing needs for intimacy, differing perceptions of the problems in the marital relationship and in each other, and differing communication styles. Our data suggest that spouses consider the lack of intimacy to be a much greater source of conflict than do the physicians, perhaps reflecting less need for spousal intimacy on the part of the physician. The physician may well feel that his or her need for intimacy-at-a-distance is satisfied through contacts with patients and colleagues. The physician may, in fact, work longer hours in order to avoid emotional closeness at home, where he or she lacks the clear role boundaries of the professional doctor-patient relationship. The spouses' concern that their physician-husbands do not talk to them enough may reflect the spouses' preference for verbal communication, while the physicians' primary complaint of insufficient sexual interest on the part of their spouses suggests a preference for nonverbal modes of expressing feelings. When the physician wishes to make love, the spouse may wish to talk. Space considerations prohibit discussion of other provocative findings from the survey, but the interested reader is referred to our forthcoming book (14). Whether the findings reported

here can be generalized to physician groups with other demographic characteristics will have to await further research.

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Effects of Amantadine and Trihexyphenidyl on Memory in Elderly Normal Volunteers

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Anticholinergic drugs impair one's ability to learn new material, even at routine clinically used doses. During the trihexyphenidyl phase of this double-blind crossover trial, elderly normal subjects complained of confusion and memory impairment and demonstrated a pattern of deficits in memory function compatible with that previously reported to result from anticholinergic drugs. The subjects neither complained of nor demonstrated memory impairment while taking amantadine, which is believed to exert its pharmacological effects upon extrapyramidal disorders via dopaminergic mechanisms and does not appear to be associated with memory impairment. Anticholinergic drugs should be avoided whenever possible in the elderly and especially in those suffering dementia.

(Am J Psychiatry 1987; 144:573–577)

Psychiatrists must be alert to pharmacological agents that adversely affect memory in late life. Neurologists and geriatricians have long believed that anticholinergic drugs used to treat patients with Parkinson's disease produce memory impairment (1). These clinical impressions first received support from studies examining the effects of atropine or scopolamine administered parenterally to normal volunteers (2–11). Subsequent systematic studies of patients with Parkinson's disease (12, 13) and of schizophrenic patients treated for the extrapyramidal side effects of neuroleptic drugs (14–16) have convincingly documented that routine clinical doses of oral anticholinergic drugs produce substantial impairment of memory.

The pattern of anticholinergic-induced memory impairment is consistent across studies. Performance on tests of immediate memory capacity, such as the digit span or word span, is not affected by anticholinergic drugs. Retrieval of information stored in memory before drug administration is only minimally sensitive to disruption by anticholinergic drugs. However, performance on tests of verbal learning of new material in which the information to be learned exceeds the memory span has been found to be impaired in virtually every study where this aspect of memory has been tested. Tests used to demonstrate this phenomenon have included free recall for lists of words, serial recall for lists of words, and learning of supraspan digit sequences. However, although recall memory (the ability to store and reproduce the stimulus material without prompts) is adversely affected by anticholinergic drugs, recognition memory (the ability to identify the stimulus material when it is presented again amidst distractors) has not, with some exceptions (17), usually been found to be impaired (18).

The pattern of memory impairment produced by anticholinergic drugs is similar to that seen in normal aging (7), and some evidence exists for alterations in the function of central cholinergic neuronal systems with increasing age (19). Two recent studies (20; Nakra et al., unpublished data) have demonstrated substantial impairment of memory in elderly normal volunteers after a single oral dose of only 2 mg of trihexyphenidyl, a standard anticholinergic drug. This pattern of memory impairment is distinct from that produced by nonspecific sedation and can be reversed by physostigmine (an acetylcholinesterase inhibitor) but not by stimulants (21).

Alzheimer-type dementia, occurring alone or in conjunction with Parkinson's disease or Down's syndrome, is associated with a profound loss of those cholinergic neurons whose cell bodies lie in the basal forebrain and whose processes extend throughout the cortical mantle (22, 23). Memory impairment is a common early sign in Alzheimer's disease, perhaps reflecting loss of the major cholinergic radiation ramifying through hippocampal structures believed to be associated with memory. Demented patients with Parkinson's disease are exquisitely susceptible to delirium when treated with anticholinergic drugs (24).

Amantadine is believed to exert its therapeutic effects on primary or neuroleptic-induced extrapyramidal disorders by stimulating the release and blocking

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Supported in part by a grant from DuPont Pharmaceuticals, Wilmington, Del.

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the reuptake of dopamine in movement-related structures and has little or no anticholinergic activity. We compared the effects of amantadine with those of trihexyphenidyl, a standard anticholinergic drug, in elderly normal volunteers to test the hypothesis that amantadine would produce significantly less impairment of memory.

METHOD

Of the 40 elderly normal volunteers who were screened for participation in the study, six never entered the drug administration phase of the trial: four of the six decided against participation and two were discovered to have medical problems that precluded their participation. After receiving active drugs, four patients were administratively removed from the evaluable cohort, two because they took concomitant medications not permitted by the protocol and two because of unexpected scheduling difficulties. All subjects provided written consent after the nature of the procedures had been fully explained to them. The remaining 30 subjects formed the evaluable cohort. The mean±SD age of this group was 66±3 years (range, 60–72 years). Seventeen were men, and 13 were women. All 30 were white.

Each subject received a 4-day trial of amantadine and a 4-day trial of trihexyphenidyl in randomized sequence under double-blind conditions. The two trials were separated by a 2-week drug-free washout period. On the morning of day 1 of a trial, subjects underwent pretrial testing on the study measures. The same evening each subject took the first trial capsule (either amantadine, 100 mg, or trihexyphenidyl, 4 mg). The principal investigator called each subject the following morning. Any subject in whom side effects were apparent after the first dose took only one capsule at bedtime for the next two evenings and one capsule with breakfast the morning of post-trial testing. The subjects without side effects took the full dose of one capsule twice daily throughout.

Five equivalent forms of the following tests were administered in randomized sequence at screening, before amantadine, after amantadine, before trihexyphenidyl, and after trihexyphenidyl.

1. Digit span forward and backward. This was a measure of the capacity of immediate memory.

2. Free recall. A list of 18 nouns was read at a constant rate to each subject, who was then asked to write down as many of them as he or she could remember. At the second through sixth trial, the subject was told only the missed words and was asked to write on a new sheet all the words he or she remembered. The total recall score was the number of words correct per list. Intrusions were words that the subject wrote down which were not part of the list.

3. Recognition-signal detection. The subjects were shown a series of 24 words. They then were shown a larger list of 48 words and were required to pick out those words which they saw before and, for each choice, rate how confident they were that their selections were correct (certain yes, probably yes, probably no, certain no), after which four summary measures were calculated: 1) hits (the rate at which subjects correctly recognize previously seen words as familiar); 2) false alarms (the rate at which subjects misperceive new words as familiar); 3) sensitivity (the rate at which subjects make correct judgments about whether words are familiar or new); and 4) response bias (the extent to which the subject favors the hypothesis that words are familiar or new, regardless of which words they are rating).

4. Retrieval-familiar categories. The subjects were given the name of a semantic category (furniture, vehicles, four-footed animals, fruits, and sports) and were asked to name in 60 seconds as many instances from the category as they could. The rater marked the list when 15, 30, 45, and 60 seconds had elapsed.

At all five time points subjects were also asked to estimate when they thought 30 seconds, 60 seconds, and 120 seconds had gone by. This was repeated three times on each occasion, and scores were the averages of the estimates made by a subject over the three repetitions. This test has been shown to be exquisitely sensitive to drug-induced changes in time perception.

The Profile of Mood States (POMS) (25), a self-administered adjective rating scale which consists of 65 items each rated from 0 (not at all) to 4 (extremely), was also completed at these time points. The subject circled the number that best described how he or she had been feeling for the past 4 days.

After the first medication trial and again after the second medication trial, the subjects completed a self-rating of memory function questionnaire (26). The subjects answered 18 questions about how their present memory ability compared to their previous memory ability (before they began the study). They circled one number from −4 (worse than ever before) to +4 (better than ever before).

At all five time points, the subjects were asked if they had any distressing symptoms. Subsequently, a 22-item side effect questionnaire was presented to the subjects. Responses of "yes" or "no" were recorded for each symptom. For "yes" responses, intensity was recorded and a clinical judgment of relationship between the occurrence of the symptom and the drug was made.

Because performance on memory testing has been shown to vary depending on time of day (27), predrug and postdrug testing were always done at the same time of day for each subject.

No information regarding side effects or dose reduction was available to the psychological examiner who administered the test batteries.

The randomized sequence, fixed-time-dependent crossover study design we used is most powerful in the situation in which order effects are small compared to main treatment effects (28). Such order effects are combined in an interaction term (Trial by Treatment)

TABLE 1. Results of Memory Tests for 30 Elderly Normal Volunteers Receiving 4-Day Trials of Amantadine or Trihexyphenidyl

	Amantadine				Trihexyphenidyl						
	Before		After		Before		After		Paired Crossover Analysis		
Memory Test	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Change[a]	t (df=28)	p
Free recall											
Trial 1, total score	5.9	1.7	6.2	1.7	6.1	1.6	3.7	1.4	2.5	6.52	<.001
Trial 2, total score	9.0	2.0	9.3	2.0	9.3	2.4	6.3	2.2	3.0	6.56	<.001
Trial 3, total score	10.5	2.2	10.8	2.4	10.5	2.7	7.8	2.3	3.0	6.12	<.001
Trial 4, total score	11.8	2.5	12.0	2.5	11.6	2.9	9.2	2.5	2.9	4.96	<.001
Trial 5, total score	12.8	2.7	12.8	2.6	12.9	2.8	9.6	2.5	3.2	7.21	<.001
Trial 6, total score	13.4	2.6	13.5	2.6	12.9	2.9	10.3	2.8	3.2	6.00	<.001
Intrusions, total score	2.3	2.5	1.9	1.7	1.9	2.5	3.5	4.8	−1.6	−2.08	<.05
Recognition-signal detection											
Sensitivity	0.91	0.06	0.92	0.05	0.91	0.06	0.88	0.06	0.04	3.82	<.01
Response bias	3.11	0.55	3.10	0.57	2.82	0.68	2.87	0.68	0.23	1.93	<.10
Hit rate	0.79	0.13	0.81	0.11	0.81	0.13	0.80	0.11	0.01	0.21	n.s.
False alarms	0.06	0.07	0.06	0.07	0.09	0.08	0.12	0.11	−0.06	−3.206	<.01
Time production											
30 seconds	34	15	30	13	35	18	25	8	5	2.85	<.01
60 seconds	70	30	61	26	71	37	52	18	9	3.20	<.01
120 seconds	131	54	118	49	138	73	111	45	17	3.19	<.01
Self-assessment											
Total score	—	—	5.13	0.75	—	—	4.67	1.26	0.46	2.69	<.05
First six questions	—	—	5.03	0.82	—	—	4.34	1.38	0.69	3.10	.01
POMS factors											
Tension-anxiety	38.2	6.0	39.0	7.0	39.4	6.6	44.6	9.5	−5.6	−3.66	<.01
Depression-dejection	39.9	4.2	38.9	2.9	39.8	5.3	40.7	4.6	−1.8	−2.27	<.05
Anger-hostility	40.3	5.1	39.2	5.1	40.3	6.0	40.0	6.9	−0.8	−0.62	n.s.
Vigor-activity	56.7	8.9	54.1	9.5	57.5	8.1	51.2	9.8	2.9	2.12	<.05
Fatigue-inertia	39.6	6.8	40.0	8.7	41.9	7.6	42.6	7.6	−2.6	−1.88	<.10
Confusion-bewilderment	38.0	5.7	38.1	6.4	37.5	6.1	45.7	10.7	−7.6	−4.02	<.001

[a]After-amantadine scores minus after-trihexyphenidyl scores; a positive number indicates that subjects scored higher while taking amantadine, and a negative number indicates that subjects scored higher while taking trihexyphenidyl.

that was estimated by the method described by Hills and Armitage (29). The main memory test outcomes were measured before the administration of the first medication; these "pre-trial-1" measures were used as covariates to increase the power to detect interactions. After the search for interactions, the results were based on the comparison of postamantadine and posttrihexyphenidyl measures. The treatment effect is defined as the average (over the two sequences) difference between the patient's postamantadine and posttrihexyphenidyl scores. These are presented as raw differences, t statistics, and p values. The p values are based on the t statistics for the Hills-Armitage method, which is equivalent to a split-plot analysis of variance of the treatments and periods (which are orthogonal in this design).

Finally, all main analyses were repeated by using only trial 1 data, as if the study were a parallel comparison (ignoring the crossover). By analysis of covariance using the pre-trial-1 scores as covariates, this fallback analysis was used to confirm the crossover analysis.

RESULTS

In 12 of the 30 subjects, dose reductions from 8 to 4 mg daily were required during the trihexyphenidyl phase of the study; in one of the 30 subjects a dose reduction from 200 to 100 mg daily was required during the amantadine phase, and one subject required dose reductions during both drug treatment phases (p=.05 for the normal approximation to the sign test of the null hypothesis of equal rates of reduction).

Examination of the main memory test outcomes revealed no evidence of effect of order of drug administration: all p values were above .40, and no interactive effect was clinically substantial. The intercorrelations among the measures across different tests never reached .6, so that no test can be entirely or even substantially replaced by another.

Paired crossover analyses comparing postamantadine and posttrihexyphenidyl measures revealed no differences between the two drug treatment phases on the digit span or categories retrieval tests. However, on the free recall test, the subjects recalled significantly fewer words and made significantly more intrusion errors while taking trihexyphenidyl than while taking amantadine (table 1). These differences in recall are entirely explainable by the impairment of memory performance when the subjects received trihexyphenidyl. While taking trihexyphenidyl, the subjects were also significantly less sensitive in discriminating between target and distractor words on a recognition memory test. As table 1 indicates, trihexyphenidyl did not reduce hits. In other words, the subjects were able to recognize recently presented words as targets. However, trihexyphenidyl increased false alarms; while

taking trihexyphenidyl, the subjects misjudged distractor words that were not in fact part of the memory list to actually be targets. By increasing false alarms, trihexyphenidyl impaired the discrimination between distractors and targets, thus lowering sensitivity. Although trihexyphenidyl did not significantly affect response bias, it tended to make the subjects less conservative in their willingness to guess that stimuli were target words ($p<.10$). Estimates of 30, 60, and 120 seconds were significantly shorter when the subjects took trihexyphenidyl.

The subjects rated their memory function as significantly more impaired while taking trihexyphenidyl than while taking amantadine and reported significantly more dysphoria and less vigor (POMS) while taking trihexyphenidyl (table 1). The covariance analysis comparing only the 15 subjects who received amantadine with the 15 subjects who received trihexyphenidyl during the first trial confirmed all of our findings.

Dry mouth was worse after trihexyphenidyl than after amantadine in 35% of the subjects, dizziness in 40%, toxic confusion in 28%, and nausea in 23%. No side effect was rated worse after amantadine than after trihexyphenidyl by more than 15% of the subjects. The only serious side effect occurred in a 70-year-old man who took the full scheduled trihexyphenidyl dose and suffered a brief anticholinergic delirium the evening before posttrial testing. He experienced illusory percepts and anxious agitation, which cleared spontaneously the next day.

DISCUSSION

In our elderly normal volunteers, trihexyphenidyl produced a pattern of memory impairment consistent with that induced by anticholinergic drugs in a variety of previously reported subject groups. Memory function after trihexyphenidyl was significantly worse than memory function after amantadine. Because there was no concurrent placebo control, we cannot state categorically that there was no impairment after amantadine.

Anticholinergic drugs decrease one's ability to enter new material into memory. Individuals thus impaired will operate at a disadvantage in a variety of occupational and social situations. They will be slow to assimilate new information or to effectively acquaint themselves with new people. Psychiatric patients may be less able to benefit from psychotherapy or vocational rehabilitation programs when receiving anticholinergic drugs. Although our subjects perceived and complained of their impairment, neuropsychiatrically ill patients may be less eloquent spokespersons of their internal experience.

Word intrusion errors, i.e., words reported during recall that were, in fact, not part of the presented list, can be induced in normal subjects by the administration of anticholinergic drugs (30). The rate at which word intrusion errors occur in patients suffering from Alzheimer's disease or postencephalitic amnesia can be diminished by the administration of cholinomimetic drugs (31). The presence of word intrusion errors in patients with dementia suggests a diagnosis of Alzheimer's disease and has been found to be associated with decreased levels of choline acetyltransferase and an increased number of senile plaques at postmortem examination of the cerebral cortex (30).

Consistent with prior reports is our finding that trihexyphenidyl did not reduce hits on a recognition memory test. However, by causing subjects to report that distractor words seemed falsely familiar, trihexyphenidyl reduced their ability to accurately discriminate between target and distractor words. The heightened tendency of subjects to make false alarms on a recognition memory test while taking trihexyphenidyl may be related to their increased propensity to make intrusion errors in a test of recall memory. Both findings suggest that anticholinergic agents may induce mild confusion about which words have recently been entered in short-term memory.

Because anticholinergic drugs usually disrupt recall but not recognition memory, some investigators have questioned whether the deficits reflect impairments in motivation and attention rather than primary memory disorder (18). The reduced ability to discriminate which words are in short-term memory cannot be simply attributed to motivational or attitudinal changes. Such extraneous changes should be reflected by alterations in the bias to report words as old or new, but trihexyphenidyl did not significantly affect response bias.

Ketchum et al. (32) reported that anticholinergic drugs produce a disturbance in the perception of time: "In mild cases, this was nothing more than a feeling that time had slipped away, or flown, during the few hours of the drug's maximal effects." The subjects estimated that 30, 60, and 120 seconds had passed significantly faster while taking trihexyphenidyl than while taking amantadine. The mean estimates were very accurate when the subjects were taking amantadine (30, 61, and 118 seconds).

The trihexyphenidyl dose used in our study (8 mg/day) was well within the dose range recommended in the 1986 edition of *Physicians' Desk Reference* and a major textbook of pharmacology (33) (1–15 mg/day). As an additional attempt to avoid excessive drug administration, we halved the dose to 4 mg/day for subjects reporting any side effects after the initial doses. The amantadine dose (200 mg/day) was the maximum usually recommended for individuals over 60 years of age; amantadine is cleared entirely by the kidneys, and renal clearance normally declines with age. We used doses of both drugs that are clinically comparable in terms of their effectiveness in treating extrapyramidal side effects (34).

We believe our results can be generalized to clinical populations. Other studies have already documented the deleterious effects of anticholinergic drugs on

memory in a variety of clinical populations. In fact, we surmise that the anticholinergic effects we have demonstrated in normal subjects will only be magnified in certain patient groups, especially those who suffer loss of cholinergic neurons.

It would seem reasonable for clinicians treating elderly patients with Parkinson's disease (especially if a concurrent dementia is present) to avoid anticholinergic drugs whenever possible and instead to use drugs that act primarily on dopaminergic neuronal systems, e.g., amantadine, bromocriptine, or L-dopa. Similarly, clinicians treating psychotic patients with neuroleptic drugs seem well-advised to use the lowest neuroleptic dose that produces an optimal therapeutic effect. Extrapyramidal side effects may not occur in some individuals at low neuroleptic doses and may be mild enough to be readily controlled by amantadine alone in others.

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Posttraumatic Stress Disorder: The Etiologic Specificity of Wartime Stressors

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The authors examined the effects of wartime stressors in a sample of 69 Vietnam veterans who were psychiatric inpatients in a Veterans Administration hospital. Participation in atrocities and the cumulative exposure to combat stressors, each independently of the other, conferred a significant risk for posttraumatic stress disorder. In contrast, the effect of these war experiences on the onset of panic, major depression, and mania was not significant. The results indicate that extreme stressors are uniquely linked with posttraumatic stress disorder's characteristic cluster of symptoms but challenge DSM-III*'s implicit assumption that the reexperienced trauma is the stressor responsible for posttraumatic stress disorder.*

(Am J Psychiatry 1987; 144:578–583)

Psychological symptoms are common sequelae of stressful experiences and adverse social circumstances (1–3). However, the etiologic role of stressors in specific psychiatric disorders, notably posttraumatic stress disorder, has been the subject of continuing controversy. The current psychiatric nomenclature, as represented in *DSM-III*, makes exposure to extreme stressors a defining feature of posttraumatic stress disorder. *DSM-III*'s text indicates that symptoms of posttraumatic stress disorder follow "a psychologically traumatic event that is generally outside the range of usual experience." Research on Vietnam veterans has emphasized the unique importance of certain types of wartime experiences for postwar adjustment (4–8). Participation in atrocities has been found to increase the risk of psychological and behavioral disturbance in veterans above and beyond the cumulative exposure to combat (7). To our knowledge, previous research has not examined the effects of war stressors—participation in atrocities or the cumulative exposure to combat—on *DSM-III*'s posttraumatic stress disorder proper. It therefore remains to be determined whether such stressors are associated distinctively with the characteristic configuration of symptoms seen in posttraumatic stress disorder or instead increase the risk of a wide range of psychological distress and psychiatric disorders, including posttraumatic stress disorder.

In this paper we examine the effects of wartime stressors in a sample of 69 Vietnam veterans who were psychiatric inpatients. We estimate the effects on posttraumatic stress disorder of 1) participation in atrocities and 2) the cumulative exposure to combat stressors. Then, we compare the effects of stressors on posttraumatic stress disorder with their effects on several other psychiatric disorders, specifically, major depression, mania, and panic disorder.

METHOD

Sample

Data analyzed in this report came from a larger study of 145 male inpatients in a large neuropsychiatric Veterans Administration medical center. All those who were psychiatric inpatients for a period of 3 months were eligible if they were between the ages of 30 and 45, did not have schizophrenia or organic brain disorder, and gave informed consent. Of the 145 veterans, 69 had served in Vietnam. Our analysis is on this subset. A methodological study to assess the performance of the diagnostic procedure was conducted with 62 of the 145 veterans. (See the following section on measurement of *DSM-III* diagnoses.) In table 1 we present the demographic characteristics of the sample of 69 Vietnam veterans. Whites outnumbered blacks, 55% (N=38) and 45% (N=31), respectively; 36% (N=25) were divorced and 10% (N=7) were separated. According to national statistics collected by the Bureau of the Census (9), 9.6% of men 30 to 44 years of age were divorced in March 1984, and 2.6% were separated. Thus, the combined percentage of divorced and separated men in our sample was

Presented at the 139th annual meeting of the American Psychiatric Association, Washington, D.C., May 10–16, 1986. Received Dec. 23, 1985; revised Sept. 12, 1986; accepted Nov. 5, 1986. From the VA Medical Center, Cleveland, Ohio. Address reprint requests to Dr. Breslau, Department of Psychiatry, Case Western Reserve University, Cleveland, OH 44106.

Supported by VA Research Division of Health Services research (Dr. Davis) and NIMH Research Scientist Award MH-00380 (Dr. Breslau).

The authors acknowledge the criticisms and suggestions of Allan Young, Ph.D., and the secretarial support of Mrs. Marilyn Roberts. Kenneth Prabucki performed the computer programming.

TABLE 1. Psychiatrists' and Lay Interviewers' Diagnoses of 62 Vietnam Veterans

DSM-III Diagnosis	Number of Diagnoses		McNemar[a]	Sensitivity	Specificity	
	Per Psychiatrist	Per Lay Interviewer	χ^2	(%)	(%)	κ
Any posttraumatic stress disorder	28	30	0.40	86	82	.67
Combat posttraumatic stress disorder	17	20	0.66	82	87	.65
Major depression	27	33	0.69	93	77	.68
Manic episode	9	17	8.00[b]	100	85	.62
Panic disorder	11	17	3.60	82	84	.54

[a]McNemar test of the significance of a departure from chance in the distribution of discrepant cases.
[b]$p<.01$, df=1.

almost fourfold that reported by the Census for men of comparable age—46% and 12.2%, respectively. While it would be desirable to compare our sample with samples similar not only in sex and age but also in social class and race composition, the marked excess of divorced and separated men in our study compared to the national sample is unlikely to be accounted for by social class differences. Sixty-six percent (N=45) had not finished high school at the time they entered military service. Most men came from working-class families: 81% (N=46) of their fathers had had manual occupations.

Measurement of DSM-III *Diagnoses*

The NIMH Diagnostic Interview Schedule (DIS) was used to ascertain the *DSM-III* diagnoses of posttraumatic stress disorder, major depression, manic episode, and panic disorder. The DIS was designed to be used by lay interviewers to elicit systematic information on signs and symptoms that form the criteria of *DSM-III* and other classification systems. Because it is a fully structured interview and because diagnoses are made by computer application of predetermined algorithms, the DIS can be expected to improve the reliability of diagnoses by reducing information and criterion variance. According to several studies in clinical and community populations, the reliability of the DIS as administered by lay interviewers compares favorably with that of other diagnostic instruments (10–13). These studies, however, did not evaluate the performance of the DIS in diagnosing posttraumatic stress disorder, since the disorder was not included in the NIMH Epidemiologic Catchment Area Program, for which the DIS was developed.

To evaluate the performance of the DIS in diagnosing *DSM-III* posttraumatic stress disorder, we replicated the methodology used in the DIS validation studies, in which the results of lay interviewers were compared with those of psychiatrists. Three psychiatrists and three lay interviewers conducted the interviews after completing equivalent training in the administration of the DIS. Sixty-two veteran psychiatric inpatients, none with a diagnosis of schizophrenia or organic brain syndrome, were interviewed by a lay interviewer and a psychiatrist, both of whom used the DIS. The time interval between the two interviews averaged 3 weeks.

The sequence of questions that covers posttraumatic stress disorder was formulated and used in the St. Louis second-wave epidemiologic catchment area survey. Respondents are first asked whether they have ever experienced something so horrible that caused symptoms of intrusive reexperiencing. A positive answer is followed by an open-ended inquiry about the nature of the traumatic event, and accounts of such events are classified into 20 precoded categories. In some types of experiences, the coding scheme allows for a separate recording of two distinct events of similar type. Some categories of trauma are abstractly defined (e.g., witnessed a close call), whereas others are concrete (e.g., disaster: dioxin; disaster: tornado). An ascertainment of a symptom of posttraumatic stress disorder in connection with an extraordinary stressor is followed by questions about whether or not each of the remaining criterion symptoms occurred subsequent to the experience of that stressor. The DIS thus produces information on stressor-specific posttraumatic stress disorder, and patients can theoretically receive up to 20 posttraumatic stress disorder diagnoses in a lifetime. For example, a person may meet the criteria for posttraumatic stress disorder in connection with a stressor coded as "physical attack on self" because of being abused as a child as well as in connection with a stressor coded as "combat" due to Vietnam war experiences.

In table 1 we present the number of lifetime diagnoses by psychiatrists and lay interviewers, the McNemar test, sensitivity, specificity, and kappa values for the disorders of interest in this report. (A total of 11 disorders were covered, however.) The McNemar chi-square was used in previous studies (11, 13) to test the statistical significance of a departure from chance in the direction of discrepant cases. It answers the following question: does one type of interviewer (psychiatrist or lay) systematically diagnose more cases as positive? For the purpose of calculating sensitivity and specificity in this study, we set the psychiatrists' DIS as the criterion against which the performance of the DIS in the hands of lay interviewers was estimated. In this analysis *DSM-III* exclusion criteria were not applied.

As can be seen in table 1, lay interviewers diagnosed three cases of combat posttraumatic stress disorder and two cases of any posttraumatic stress disorder in excess of the psychiatrists. The difference in either diagnosis was not statistically significant. The tendency of lay interviewers to make more diagnoses was marked and statistically significant for manic episode: the lay interviewers diagnosed almost twice as many cases.

Kappas for any posttraumatic stress disorder and for combat posttraumatic stress disorder were, at .67 and .65, among the highest found in this study. They also compared favorably with kappas for other *DSM-III* diagnoses reported by Robins et al. (11). The mean kappa in that study was .69, a figure only slightly higher than the kappas for the two posttraumatic stress disorder diagnoses. Our results on other disorders were also similar to those reported by Robins et al. For example, in our study, kappas for major depression and manic episode were .68 and .62, respectively, whereas in Robins et al.'s study, kappas were .63 and .65, respectively. Sensitivity for the diagnosis of any posttraumatic stress disorder was 86% and for combat posttraumatic stress disorder, 82%. Specificity was 82% for any posttraumatic stress disorder and 87% for combat posttraumatic stress disorder.

A comparison of our results on all disorders with the results reported by Robins et al. (11) reveals that whereas in our study sensitivity generally exceeded specificity, in the Robins study the opposite was true. This discrepancy is undoubtedly due to the difference in the lay interviewers' bias between the two studies, namely to "overdiagnose" in our study and "underdiagnose" in the Robins study. Mean sensitivity in our study was 88% and mean specificity was 78%, compared with 75% and 94%, respectively, in the Robins study.

In sum, our data show good concordance between lay interviewers' and psychiatrists' diagnosis of *DSM-III* posttraumatic stress disorder when both used the DIS. Although lay interviewers diagnosed slightly more cases than psychiatrists did, the differences in the rates of diagnoses were not significant, and kappas, measuring agreement between lay interviewers and psychiatrists, were relatively high. When the psychiatrists' diagnoses were defined as the criteria against which lay interviewers' accuracy was measured, the sensitivity of the DIS posttraumatic stress disorder was slightly lower but specificity was higher, compared to the figures for other disorders in our study.

Measurement of War Stressors

A separate interview schedule, administered before the DIS, elicited information on demographic characteristics, military experience, and pre- and postservice history. Seven items, taken from Robins (14), inquired about the following combat experiences: "enemy fire," "wounded," "attached to a unit in the South Vietnamese army," "surrounded by the enemy," "separated from unit," "combat patrol," and "buddy killed in action." The seven items form an additive scale, which measures the number of combat stressors a veteran had experienced and has an internal consistency reliability (Cronbach's alpha) of .73. Because some reports (7, 8) have underscored the importance of soldiers' involvement in abusive violence, we included two additional items, one on witnessing and the other on participating in atrocities. (See appendix 1 for the nine items.)

TABLE 2. War Stressor Risk Factors for Combat Posttraumatic Stress Disorder Among Vietnam Veterans

			Subjects With Posttraumatic Stress Disorder (N=69)				
	Subjects Reporting Stressor		Exposed to Stressor		Not Exposed to Stressor		
Stressor	N	%	N	%	N	%	p
Under enemy fire	64	93	42	66	2	40	<.50
Buddy killed in action	56	81	41	73	3	23	<.002[a]
Combat patrol/ dangerous duty	55	80	38	69	6	43	<.13
Surrounded by the enemy	53	77	37	70	7	44	<.10
Witnessed atrocities	50	73	38	76	6	32	<.002[a]
Separated from unit	31	45	26	84	18	47	<.004[a]
Participated in atrocities	27	39	27	100	18	43	<.0000[a]
Attached to a unit in the South Vietnamese army	27	39	22	82	22	52	<.028
Wounded	23	33	15	65	29	63	<1.00

[a]Statistically significant at alpha set to correct for multiple interrelated tests (.005).

RESULTS

The rate of *DSM-III* posttraumatic stress disorder in the sample of 69 psychiatric inpatients who were Vietnam veterans was 77% (N=53), and the rate of combat posttraumatic stress disorder was 68% (N=47). Most of those with combat posttraumatic stress disorder (82.5%, N=39) experienced characteristic symptoms at the time of the interview or within 4 weeks before the interview, whereas in 17.5% (N=8), the characteristic symptoms were in remission. Only a small fraction (21%, N=11) fell into the "delayed" subtype of posttraumatic stress disorder, that is, with symptom onset more than 6 months after the trauma. Eighty percent of the sample (N=55) met *DSM-III* criteria for major depression, 44% (N=30) for mania, and 32% (N=22) for panic disorder. The rates of *DSM-III* disorders of substance abuse and dependence were very high—86% (N=59) and 81% (N=56) for drug and alcohol, respectively.

In table 2, we show the percent of the sample reporting each of the nine wartime stressors. Most veterans in the sample (73% to 93%) reported that they had experienced the following: "enemy fire," "buddy killed in action," "combat patrol and other dangerous missions," "surrounded by the enemy," and "witnessed atrocities." Only a minority (33% to 45%) reported the following: "separated from unit," "participated in atrocities," "attached to a unit in the South Vietnamese army," or "wounded." Table 2 also presents the data on the risk of posttraumatic stress disorder associated with exposure to each stressor. These are displayed as the proportions of diagnoses of posttraumatic stress disorder in patients who were exposed and patients who were unexposed to each stressor. Thus, for example, the risk for posttraumatic stress disorder associated with having been under enemy fire was 66% versus 40% (or a relative risk of 1.6). As can be seen, the risk of posttraumatic stress disorder varied widely across stressors, reaching statistical significance in the case of "buddy killed in action," "witnessed atrocities," "separated from unit," and "participated in atrocities" (with relative risks of 1.8 to 3.1).

Because combat assignment exposed soldiers to a variety of traumatic events, stressors were intercorrelated. We therefore examined the risk for posttraumatic stress disorder associated with individual stressors, controlling for the effects of other stressors with which they were correlated. We found, for example, that the relationship between witnessing atrocities and posttraumatic stress disorder was accounted for by the effect of participation in atrocities, a stressor with which it had a moderately positive correlation (r=.43). The proportion of diagnoses of posttraumatic stress disorder among veterans who witnessed but did not participate in atrocities was not higher than the proportion among veterans who neither participated in nor witnessed atrocities—56% (N=13) and 53% (N=10), respectively. In contrast, the rate of posttraumatic stress disorder among those who participated in atrocities was 100%. The finding that participation in atrocities conferred a strong risk for posttraumatic stress disorder had to be put to further test because those who reported this stressor had, on the average, more *combat* stressors than those who did not—5.3 and 3.9, respectively (t=3.39, df=67, p<.001).

A hierarchical multiple regression analysis was performed to estimate the independent effects of 1) participation in atrocities and 2) number of combat stressors on posttraumatic stress disorder. The results appear in table 3. Posttraumatic stress disorder (present or absent) was regressed in the first step on participation in atrocities (yes or no). The regression slope was statistically significant and accounted for 29% of the variance in posttraumatic stress disorder. In the second step, number of combat stressors was added and the regression was recalculated. The partial regressions of the two independent variables were

TABLE 3. Hierarchical Regression Analysis of Combat Posttraumatic Stress Disorder on Participation in Atrocities and Number of Combat Stressors for 69 Vietnam Veterans

Independent Variable	B[a]	
	Step 1[b]	Step 2[b]
Participated in atrocities (yes/no)	.534[c]	.423[c]
Number of combat stressors	—	.062[c]
R^2	.29	.35

[a]Unstandardized regression.
[b]In step 1, only participation in atrocities was entered; in step 2, both participation in atrocities and number of combat stressors were entered.
[c]Coefficient exceeds twice its standard error.

significant, and together they accounted for 35% of the variance in posttraumatic stress disorder.

Posttraumatic stress disorder, the dependent variable, was measured as a dichotomous variable and was scored 1 if a respondent met the criteria for the disorder, 0 if not. The predicted value of this variable may be interpreted as the probability that a respondent had posttraumatic stress disorder, given the values of the independent variables. There are some statistical problems associated with the use of a dichotomous dependent variable in ordinary least squares regression. However, because alternative methods, such as Probit analysis, have been shown to produce results that are not materially different from ordinary least squares, the latter technique is used here. Note also that as the split of the dichotomous dependent variable is within a reasonable distance from the midpoint (69% with posttraumatic stress disorder and 31% without posttraumatic stress disorder), violating the assumptions in ordinary least squares regression analysis is unlikely to have material consequences. Similar considerations apply in the remaining three regressions.

The experience of participation in atrocities had an independent effect on posttraumatic stress disorder when the number of combat stressors was controlled for. It increased by 42% the probability of a veteran in this sample being given a diagnosis of posttraumatic stress disorder. The increment in the probability of posttraumatic stress disorder being associated with each combat stressor, when participation in atrocities was controlled for, was 6%. These findings support the hypothesis that participation in atrocities conferred a uniquely strong risk for posttraumatic stress disorder. They show, additionally, that the risk for posttraumatic stress disorder was associated with the cumulative exposure to varied combat experiences.

To describe more clearly the alternative paths to posttraumatic stress disorder—participation in atrocities or cumulative combat events—we present in table 4 the proportion of diagnoses of posttraumatic stress disorder associated with various levels of war stressors for those who did and those who did not participate in atrocities. Among patients who did not participate in

TABLE 4. War Stressors and Posttraumatic Stress Disorder in 69 Vietnam Veterans Who Did Or Did Not Participate in Atrocities

Number of Stressors[a]	Posttraumatic Stress Disorder: Yes N	Yes %	No N	No %
Did not participate in atrocities (N=42)				
0–3	3	23	10	77
4–6	12	52	11	48
7 or 8	5	83	1	17
Participated in atrocities (N=27)				
0–3	2	100	0	0
4–6	10	100	0	0
7 or 8	15	100	0	0

[a]Stressors were the following: under enemy fire; wounded in combat, attached to a unit in the South Vietnamese army, surrounded by enemy, separated from unit, combat patrol/dangerous duty, buddy killed in action, witnessed atrocities.

TABLE 5. Hierarchical Regression Analyses of Posttraumatic Stress Disorder, Panic Disorder, Major Depression, and Manic Episode on Participation in Atrocities and Number of Combat Stressors for 69 Vietnam Veterans

Independent Variable	B[a]: Posttraumatic Stress Disorder	Panic Disorder	Major Depression	Manic Episode
Participated in atrocities (yes/no)	.423[b]	.161	.113	.092
Number of combat stressors	.062[b]	.060[b]	.033	.025
R^2	.35	.13	.09	.03

[a]Unstandardized regression.
[b]Coefficient exceeds twice its standard error.

atrocities, 23% of those reporting zero to three stressors had posttraumatic stress disorder. The proportion of posttraumatic stress disorder rose to 83% among those with seven to eight stressors.

To examine whether war stressors were distinctively associated with posttraumatic stress disorder or instead increased the risk for other disorders as well, hierarchical multiple regressions were also performed for panic disorder, major depression, and manic episode as dependent variables, with participation in atrocities and number of combat stressors as the independent variables. In table 5, we compare the posttraumatic stress disorder regression with the three additional regressions. As can be seen, neither major depression nor manic episode had significant regression slopes on either of the stressor variables, and the amounts of variance explained were small—9% in major depression and 3% in manic episode. The results for panic disorder were less clear-cut: while the variance accounted for by the two stressor variables was far smaller than in posttraumatic stress disorder and the impact of participation in atrocities was not significant, the effect of number of combat stressors was significant and similar in magnitude to that in the posttraumatic stress disorder regression.

DISCUSSION

Our analysis suggests a distinctively marked association between war stressors and posttraumatic stress disorder in this sample of psychiatrically hospitalized Vietnam veterans. Participation in atrocities and number of combat stressors, each independently of the other, conferred a significant risk for posttraumatic stress disorder. In contrast, the effects of war stressors on the onset of panic disorder, major depression, and manic episode were, by and large, insignificant. Note that these three psychiatric disorders constitute theoretically relevant diagnoses for testing the etiologic specificity of extreme stressors. They represent the affective and anxiety disorders with which posttraumatic stress disorder as a diagnostic entity is most likely to be confounded, since *DSM-III*'s criteria for posttraumatic stress disorder include symptoms that are also characteristic of affective and anxiety disorders. Although the rates of other psychiatric disorders, such as substance abuse, in patients with posttraumatic stress disorder are high, our concern is with those diagnostic categories defined in *DSM-III* by sets of symptoms that overlap with the symptoms that define posttraumatic stress disorder (15). Moreover, in the patient population of this study, the subset of Vietnam veterans had higher rates of posttraumatic stress disorder, panic disorder, major depression, and manic episode than the subset of patients who did not serve in Vietnam. The rates of other disorders were similar in the two patient groups.

The finding that participation in atrocities markedly increased the risk of posttraumatic stress disorder replicates previous findings reported by Laufer et al. (7). Those researchers used a more extensive list of combat stressors. Their 10-item scale had a slightly higher reliability than the seven-item scale we used (.83 versus .73), a difference due chiefly to the greater number of items; the mean intercorrelation among the items in the two scales was similar (.29 and .33). The consistency of the results of the two studies, despite differences in the measurement instrument, supports the theoretical generalizability of the findings. Moreover, the results of this study take us a step further in that they indicate that participation in atrocities increases the risk for posttraumatic stress disorder as a distinct diagnosis and not simply the risk for other psychiatric disorders, such as affective illness and panic disorder. These results support the validity of some elements of *DSM-III*'s definition of posttraumatic stress disorder. Specifically, they show that extreme stressors are uniquely linked with the characteristic cluster of symptoms of posttraumatic stress disorder. However, even as they support a distinctive relationship between extreme stressors and posttraumatic stress disorder, they challenge *DSM-III*'s implicit assumption that the reexperienced trauma is the stressor

responsible for posttraumatic stress disorder. The data indicate that the risk of this disorder increased with the number of stressful combat events that veterans reported on an inventory covering combat history. Thus, the risk of the disorder in exposed veterans is not necessarily a function of the "reexperienced" trauma. Our interpretation of this point is consistent with the psychoanalytic construct of "screen" memory, which postulates that the selected critical event substitutes for other, less tolerable experiences that remain hidden (16). This concept has been elaborated in connection with posttraumatic stress disorder by several investigators (see the review by Brett and Ostroff [17]).

As in other studies, the generalizability of the results is limited by the characteristics of the sample, which in this study comprised psychiatrically hospitalized Vietnam veterans. The limitation applies primarily to the estimated risks of posttraumatic stress disorder (and other psychiatric disorders) associated with the exposure to wartime stressors. Clearly, an unbiased assessment of these risks would require a sample of Vietnam veterans who were exposed to war stressors, rather than veterans in psychiatric treatment. Undoubtedly, our estimates of the psychiatric risk associated with participation in atrocities, or with combat stressors, overstate the true risks associated with these experiences in the population of exposed veterans.

The limitation imposed by the characteristics of our sample of patients does not, however, extend to the findings about the relative weight of war stressors in predicting posttraumatic stress disorder in contrast to other psychiatric disorders. In other words, the finding that stressors have a distinctive connection with posttraumatic stress disorder is far less likely to be the result of sampling. The latter finding, nonetheless, must be interpreted cautiously. Future research should attempt to determine whether the stressor connection to *DSM-III*'s configuration of symptoms of posttraumatic stress disorder, especially in the chronic and delayed subtypes, is truly causal or instead represents patients' construction of historical and symptomatic experiences into coherent and personally meaningful accounts.

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APPENDIX 1. Interview Schedule Items Measuring War Stressors in a Sample of Vietnam Veterans

1. While you were in Vietnam, were you ever under enemy fire?
2. Were you ever wounded in a combat operation?
3. Were you ever in a unit attached to the South Vietnamese army?
4. Were you ever stationed in a location that was surrounded by the enemy?
5. Were you ever separated off from the main body of your unit?
6. Did you go on combat patrols or have other very dangerous duty while in Vietnam?
7. While you were in Vietnam, did any close friend or buddy of yours there get killed in combat?
8. While you were in Vietnam, did you see atrocities such as torture, mutilation, or severe mistreatment of military personnel or civilians?
9. While you were in Vietnam, did you participate in atrocities such as torture, mutilation, or severe mistreatment of military personnel or civilians?

Psychiatric Disorders in a Community Sample of Adolescents

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The prevalence of psychiatric disorders diagnosed according to DSM-III *in adolescents in the general population is not known. The authors address this issue in a community sample of 150 adolescents 14–16 years of age. Structured interviews as well as other instruments were used to collect data. Twenty-eight (18.7%) of the 150 adolescents were identified as having a psychiatric disorder. These 28 adolescents viewed their parents as less caring, had lower self-esteem, and resolved their conflicts through verbal aggression and physical violence more often than did the adolescents who did not have a psychiatric disorder. The authors make recommendations regarding the use of structured interviews in future research.*

(Am J Psychiatry 1987; 144:584–589

Only a limited number of studies have addressed the prevalence of psychiatric disorders in community samples of adolescents (1). In Australia, Krupinski et al. (2) and Henderson et al. (3) used medical students to interview all families in a small town to determine the prevalence of all forms of medical disability. They reported some type of psychiatric disorder in about 10% of the children and 16% of the adolescents. Unfortunately, the criteria for disorders were not specifically defined. Leslie (4) made a psychiatric assessment of 141 adolescents 13 and 14 years old in Blackburn, an industrial town in northern England. The diagnoses, however, were globally categorized into neurotic, conduct, and mixed disorders; the total prevalence rates for boys and girls were reported to be 21% and 14%, respectively. Lavik (5) compared adolescents who resided in a suburb of Oslo with another group from a rural area in southwest Norway and reported that suburban adolescents had significantly more psychiatric disorders.

In the Isle of Wight study (1, 6, 7), it was reported that psychiatric disorders at age 14 were similar in many respects to those reported at age 10, with the exception of depression, which was much more common in the adolescent sample. Overall, psychiatric disorders were slightly more common in adolescence than in middle childhood. Considering various sources of data collection, the authors estimated that the 1-year period prevalence of psychiatric disorders in adolescents was 21%.

It is noteworthy that all of these studies were conducted outside the United States. Furthermore, most of them used a very global system of diagnostic classification (e.g., neurotic, conduct, and mixed disorders). In addition, all of these studies were conducted before the development of *DSM-III*.

In the United States, Myers et al. (8) found that the 6-month prevalence rate of adult psychiatric disorders in three communities was substantially higher for people under the age of 45. Rates were about two times higher for individuals younger than 45 years of age than for those 45 years of age and older. Further comparisons revealed that in all three communities the prevalence of *DSM-III* disorders was higher in subjects between the ages of 18 and 24 years. This is an interesting finding, since it identifies younger adults and some teen-agers (18- and 19-year-olds) as a group with the highest prevalence of psychiatric disorders. Because this study did not include subjects under age 18, the prevalence of psychiatric disorders in the younger age group remains unknown.

The present study was designed to determine 1) the prevalence of psychiatric disorders in an adolescent population and the coexistence of various *DSM-III* diagnoses, 2) correlations between psychiatric disorders and sex, age, and other demographic characteristics, such as having lived in a broken home, 3) conflict resolution in the group with psychiatric disorders and the association between physical abuse and psychopathology, 4) the relationship between self-concept and psychiatric disorders, 5) how adolescents with psychiatric disorders view their parents, and 6) some general issues relevant to the mental health of adolescents, such as sexual relations and smoking.

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METHOD

Subjects in this study were 150 adolescents 14–16 years of age; they represented 7% of all adolescents in this age group attending public schools in Columbia, Mo. Subjects' names were initially drawn in a systematic manner to obtain equal numbers in each age group (50 in each) and an equal number of boys and girls (75 of each). The sample size was essentially determined by budgeting limitations. There were 142 Caucasian, six black, and two Oriental adolescents in the sample. According to Hollingshead and Redlich's social class criteria (9), 16 (10.7%) were in class I, 47 (31.3%) were in class II, 44 (29.3%) were in class III, 41 (27.3%) were in class IV, and two (1.3%) were in class V.

Procedure

Subjects' participation was solicited by phone. Data on each subject were obtained during a home interview and by means of mail-in questionnaires. During the home visit, the adolescent and one parent were each given a structured psychiatric interview, including the Diagnostic Interview for Children and Adolescents and the Diagnostic Interview for Children and Adolescents–Parent Version (10, 11). Each parent also completed the Child Behavior Profile (12, 13) and gave information regarding socioeconomic and marital status during the home visit. Likewise, each adolescent completed a set of questionnaires, including the Parental Bonding Instrument (14), the Conflict Resolution Scale (15), and the Piers-Harris Children's Self-Concept Scale (16).

Three clinicians with master's degrees who were doctoral candidates in psychology (C.F., C.M.C., and J.A.M.) served as data collectors. Their training followed the general format used in several of our past studies at the University of Missouri. To describe the method briefly, all interviewers first underwent a training program in administration of the Diagnostic Interview for Children and Adolescents and the Diagnostic Interview for Children and Adolescents–Parent Version. As part of this training, each clinician-interviewer conducted several interviews while being videotaped. These videotapes were then observed by the other two clinicians, as well as the senior investigators (J.H.K. and N.C.B.). Interrater reliability training was accomplished by having the interviewers fill out Diagnostic Interview for Children and Adolescents and Diagnostic Interview for Children and Adolescents–Parent Version forms while observing the videotaped interviews. This was followed by a series of group meetings during which correspondence between ratings as well as disparate scores were reviewed in detail. Actual study interviews did not take place until each interviewer pair had achieved an interrater agreement rating of at least 95%. For the first 20 subjects, each interviewing clinician was observed by one of the other two clinicians, who also recorded the subject's responses. Subsequently, ongoing supervision of recorded responses was conducted and regular retraining exercises were held every 30–50 interviews to minimize rater drift (17).

Every effort was made to keep the refusal rate low. Of 214 individuals solicited by phone, 115 (72.4%) agreed to participate. Information with which to calculate socioeconomic status scores was obtained for 41. The mean socioeconomic status level for these 41 adolescents was 2.98; for the 150 participants it was 2.77. The difference between groups was not significant (Mann-Whitney U test).

We developed a 4-point scale to rate generalized dysfunction and the need for treatment of adolescents: 1=healthy—no need for treatment, 2=mildly impaired—might benefit from treatment, 3=moderately impaired—definite need for treatment, and 4=severely impaired—serious need for treatment. The rating was made and recorded by the clinician at the end of the interview, along with her clinical impression regarding the subject's diagnosis. Only those individuals with ratings of 3 or 4 were considered as needing treatment; subjects with ratings of 1 or 2 were categorized as not needing treatment.

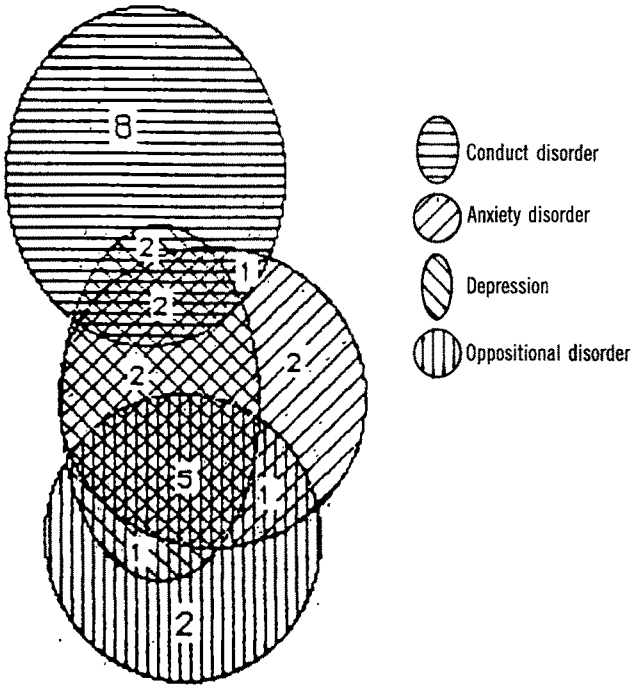
Definition of "Caseness"

Since "caseness" in the general population is neither assumed nor implied, a precise definition of "caseness" was among our most important tasks (18; unpublished 1969 paper of Dohrenwend et al.). However, due to the lack of observable or measurable physical representation of psychiatric disorders, "caseness" inevitably derives from psychiatric opinion and clinical experience (19).

Since meeting the criteria for a disorder does not necessarily imply a concomitant need for treatment, we decided to accept as "cases" only those individuals who not only met *DSM-III* criteria for a disorder but also were rated as needing treatment. Taking into account that the need for treatment is dependent on the clinician's opinion, we decided to accept as valid only those "cases" where two independent judges agreed that an individual needed intervention.

In the present study, at the conclusion of each interview the clinician used her clinical judgment to determine probable diagnoses and the need for treatment for that particular subject. In addition, a child psychiatrist (J.H.K.) reviewed all of the child and parent responses on the Diagnostic Interview for Children and Adolescents and the Diagnostic Interview for Children and Adolescents–Parent Version. However, he was unaware of the results of other measures. On the basis of this information and his clinical judgment, the psychiatrist made a recommendation as to whether the subject needed treatment. Although a decision as to "caseness" was made after the information from the parents was also obtained, the final diagnosis was based on the Diagnostic Interview for Children and Adolescents. This approach is in line with recent work

FIGURE 1. Overlap of Four Most Common Diagnoses Among 28 Adolescents With Psychiatric Disorders[a]



[a]Conduct disorder and oppositional disorder do not overlap because *DSM-III* states that subjects meeting criteria for conduct disorder should not be diagnosed as having oppositional disorder.

by Edelbrock et al. (20), who found that the reliability of the child increased sharply with age and, conversely, that the reliability of the parent's report decreased with the age of the child.

Two-way contingency tables were analyzed by chi-square or by Fisher's exact tests if the number of observations was small. Tests for location were Wilcoxon-Mann-Whitney U tests. Confidence intervals for proportions were determined by approximating a binomial distribution rather than by adding and subtracting a constant times the standard error from the proportion.

RESULTS

Sixty-two (41.3%) of the 150 adolescents were found to have at least one *DSM-III* diagnosis based on the Diagnostic Interview for Children and Adolescents without the criteria of impaired functioning and the need for treatment. When these additional criteria were used (as agreed on by at least two independent clinicians, the interviewer, and the child psychiatrist), 28 adolescents (12 boys and 16 girls) were identified as having a psychiatric disorder, yielding a current point prevalence rate of 18.7%. A total of 67 diagnoses were made: seven of the adolescents had only one disorder, 10 had two, four had three, and seven had four; the mean number of diagnoses was 2.4. Figure 1 illustrates interrelationships among the four most common diagnoses, anxiety disorder, conduct disorder, depression, and oppositional disorder. The only diagnoses for which there were significantly different intersex prevalence rates were depression and anxiety disorders. Table 1 shows the diagnoses made in the order of their prevalence. The three most common diagnoses were conduct disorder, anxiety disorder, and depression.

A number of variables that were collected showed no relation with psychiatric disorder in adolescents. For example, the association between adolescents with psychiatric disorder and sex was not significant. Sixteen (57%) of the 28 adolescents with a psychiatric disorder were girls; 59 (48%) of the 122 adolescents without disorder were girls ($\chi^2=0.70$, df=1, n.s.). Likewise, the socioeconomic status of the family and race failed to distinguish adolescents with psychiatric disorder. The mean socioeconomic status level of the adolescents with disorders was 2.9, compared with 2.7 for the rest of the sample. Divorce or parental separation did not significantly distinguish the two groups either. Eight (29%) of the 28 diagnosed adolescents and 29 (24%) of the remaining 122 adolescents reported such a history ($\chi^2=0.28$, df=1, n.s.). A history of behavior disorder dating back to preschool years (obtained from the Diagnostic Interview for Children and Adolescents–Parent Version) was reported by the parents of diagnosed adolescents more frequently than by those of the rest of the sample. However, the difference was not statistically significant: 11 (39.3%) of the adolescents with psychiatric disorder and 31 (25.4%) of those without reported such a history ($\chi^2=2.19$, df=1, n.s.).

Other variables, however, did correlate positively with psychiatric disorder. Physical abuse significantly distinguished the two groups: 12 (43%) of the adolescents with but only six (5%) of those without reported severe beating that left marks and bruises (Fisher's exact test, $p<.0001$). An association also emerged between psychiatric disorder and sexual relationships. Fifteen (54%) of the adolescents with disorders but only 21 (17%) of the remaining sample reported having had sexual relations with at least one partner by the time of this study ($\chi^2=16.5$, df=1, $p<.0001$). The same held true for cigarette smoking. Thirteen (46%) of the diagnosed adolescents reported smoking daily for at least 1 or more months, versus only five (4%) of the remaining sample (Fisher's exact test, $p<.0001$).

Adolescents with psychiatric disorders differed from those without in their methods of conflict resolution (15). The diagnosed adolescents reported resolving their conflicts significantly more frequently through verbal aggression and physical violence than did the rest of the sample (table 2). In regard to self-concept, adolescents with disorders had significantly lower self-concepts according to the Piers-Harris Scale (19) (table 2). The Parental Bonding Instrument, which attempts to assess parental styles of child rearing, also served to distinguish adolescents with psychiatric disorders from those without. The mean±SD care factor score of the

TABLE 1. Prevalence of Psychiatric Disorders in 150 Adolescents

DSM-III Diagnosis	Boys (N=75) N	%	Girls (N=75) N	%	Total (N=150) N	%	95% Confidence Intervals Lower	Upper
Anxiety disorder	3	4.0	10[a]	13.3	13	8.7	4.9	14.7
Conduct disorder	7	9.3	6	8.0	13	8.7	4.9	14.7
Depression (major depression and dysthymic disorder)	2	2.7	10[b]	13.3	12	8.0	4.4	13.9
Oppositional disorder	3	4.0	6	8.0	9	6.0	3.0	11.4
Both alcohol and drug abuse or dependence	5	6.7	4	5.3	9	6.0	3.0	11.4
Drug abuse or dependence	4	5.3	4	5.3	8	5.3	2.5	10.5
Alcohol abuse or dependence	3	4.0	2	2.7	5	3.3	1.2	8.0
Attention deficit disorder	1	1.3	2	2.7	3	2.0	0.5	6.2
Somatization disorder	1	1.3	1	1.3	2	1.3	0.2	5.2
Mania	0	0.0	1	1.3	1	0.7	0.0	4.3
Enuresis	0	0.0	1	1.3	1	0.7	0.0	4.3
Anorexia or bulimia	0	0.0	0	0.0	0	0.0	0.0	0.0

[a]Significantly more girls than boys had this diagnosis (Fisher exact p=.03).
[b]Significantly more girls than boys had this diagnosis (Fisher exact p=.02).

TABLE 2. Conflict Resolution and Self-Concept Scores of Adolescents With (N=28) and Without (N=122) Psychiatric Disorders

Measure	Score: Adolescents With Psychiatric Diagnoses Mean	SD	Adolescents Without Psychiatric Diagnoses Mean	SD	p[a]
Conflict Resolution Scale[b]					
Reasoning subscale (range=0–18)	11.1	4.1	11.7	3.2	n.s.
Verbal aggression subscale (range=0–36)	20.6	7.5	14.4	5.7	.0001
Physical violence subscale (range=0–48)	16.4	9.6	10.1	4.7	.0001
Piers-Harris Children's Self-Concept Scale[c]					
Behavior (range=0–18)	10.8	3.4	15.3	3.3	.0001
Intellect (range=0–18)	10.9	4.0	14.1	3.3	.0001
Physical appearance (range=0–12)	7.5	3.0	8.7	2.8	.05
Anxiety (range=0–12)	6.7	2.4	8.7	2.6	.0001
Popularity (range=0–12)	8.2	3.0	9.5	2.5	.03
Happiness, satisfaction (range=0–9)	5.5	2.6	7.0	2.0	.003
Total raw score (range=0–80)	48.6	13.5	61.5	12.2	.0001

[a]Mann-Whitney U test.
[b]A higher score on any subscale indicates a greater use of the item listed.
[c]Greater self-concept is indicated by a lower score on the anxiety item and higher scores on the other items.

former was 22.8±7.8, while it was 28.4±6.8 for the latter (p<.0003, Mann-Whitney U test).

Finally, the parental report data from the Child Behavior Profile (12, 13) indicated that the boys with psychiatric disorder were given higher "externalizer" ratings (62.5±12.3) than boys without disorder (52.0±8.8) (p<.002, Mann-Whitney U test). They were also more aggressive, hyperactive, and hostile or withdrawn than the boys without disorder. Alternatively, girls with psychiatric disorder were reported to have more somatic complaints (66.4±6.6) than girls without disorder (62.3±7.4) (p<.03, Mann-Whitney U test).

DISCUSSION

This study described strategies and methods crucial to conducting epidemiological studies in the general population. These include the definition of "caseness," problems of using structured interviews, training the interviewers, the importance of rating the severity of adolescent dysfunction, and the need for psychiatric intervention. The major findings of this study may be summarized as follows:

1. Twenty-eight (18.7%) of 150 adolescents from a nonreferred sample were found to have at least one *DSM-III* diagnosis, were functionally impaired, and were judged to need treatment. The three most common diagnoses were anxiety disorder, conduct disorder, and depression.

2. A history of physical abuse distinguished the group of adolescents with psychiatric disorders from those without psychiatric disorders. At the same time, the adolescents with disorders reported a tendency to resort more frequently to verbal aggression and physical violence to resolve conflicts.

3. A history of initiating sexual relations and smok-

ing by age 14–16 was seen more often in adolescents with than in those without psychiatric disorder.

4. In addition to having a low self-concept, boys with psychiatric disorders were frequently described by their parents as externalizers, while somatic complaints were reported more frequently among girls with disorders.

5. The parents of adolescents with psychiatric disorders were described as significantly less caring than were the parents of adolescents without psychiatric disorders.

Several of this study's limitations need to be acknowledged. Due to the small sample size this study should be considered a pilot and preliminary attempt to answer the questions raised. Although structured interviews have improved data collection and reliability in child and adolescent psychiatric investigations, several recent studies have suggested that structured interviews designed for clinical samples might lead to overestimation of the reported prevalence in the general population (21; Patricia Cohen, 1986 personal communication). Lerner et al. (22) used the Diagnostic Interview for Children and Adolescents in a follow-up study of 88 children and stated that "using *DSM-III* (or instruments based on DSM-III criteria) for general population screening may overestimate the true prevalence of psychiatric disorder." To circumvent this bias, in this study we not only used a scale for severity but also considered impairment of functioning and the need for treatment.

Because our sample did not include mentally retarded or institutionalized adolescents, the findings cannot be generalized to these groups. Additionally, the measures used did not tap organic dysfunction and intellectual level. We also recognize that mild cases of some conditions were not included in the prevalence data—for example, anxiety disorders (with a severity rating of 2). However, at this preliminary stage, data concerning the frequency of *DSM-III* psychiatric disorders in adolescents from the community are sparse, and we preferred to be conservative rather than overinclusive. Regarding the prevalence of psychiatric disorders in adolescents, to our knowledge there are no similar published studies of adolescents using a structured interview based on *DSM-III* criteria, although Offer's estimate (23) that 20% of the adolescents in our culture are considered disturbed approximates our findings. The only study with which we could attempt comparison was an adult NIMH-supported study by Myers et al. (8) However, several important differences distinguish our study from theirs. Perhaps most important, a *DSM-III* diagnosis was necessary but not sufficient for "caseness" in our study. Further, we relied on trained mental health professionals rather than lay personnel to interview our subjects, and agreement of at least two mental health professionals was required for both a diagnosis and the presence of "caseness." Myers et al. found phobia, alcohol abuse, and depression to be the three most prevalent psychiatric disorders; in our study, the three most common diagnoses were anxiety disorder, conduct disorder, and depression.

We found significantly different intersex prevalence rates for only two diagnoses, anxiety disorder and depression, both of which were higher in girls. *DSM-III* considers anxiety, panic attacks, and phobias as associated features of major depression. In this study we found that depression and anxiety disorder coexisted (figure 1). However, it was not possible to distinguish primary from associated conditions.

The significant relationship between "caseness" and exposure to physical violence is of interest. The adolescents with psychiatric disorders used verbal aggression and physical violence to resolve conflicts. Their previous victimization by violence may have been adopted as a model by which they resolved future conflicts with others.

The Parental Bonding Instrument, which measures qualitative aspects of the parent-child relationship and parental styles, supported the diagnosed adolescents' perception that they were not wanted. The care factor, which assesses the degree of affection, emotional warmth, empathy, and closeness at one pole, and emotional coldness, indifference, rejection, and neglect at the other, significantly distinguished adolescents with and without psychiatric disorders. According to the diagnosed adolescents, their parents seldom smiled at, talked with, or praised them. They also reported that their parents failed to console them when they were upset, recognize their needs, make them feel wanted, show understanding, or extend a helping hand. Therefore, the data provide further evidence for the importance of parental care and its relationship to the existence or absence of psychiatric disorders.

It is also interesting to note that not only were the total raw scores on the Piers-Harris Children's Self-Concept Scale significantly lower among the adolescents with psychiatric diagnoses, but also all of this instrument's subscales (factors) exposed significant differences between the two groups. Factors 1 and 2 indicated that the diagnosed adolescents perceived their behavior and intellectual ability as lower than those of other children their age. Factors 3 and 4 suggested that they did not see themselves as having substantial status among peers and that they were anxious, while factors 5 and 6 indicated that they did not feel they were wanted by others and were not satisfied with life. Such findings have clinical implications for the treatment of disturbed adolescents—treatment methods need to be directed at improving adolescents' self-concept.

In terms of future research, we suggest that severity ratings as well as ratings of impaired functioning and/or the need for treatment be made by trained professionals. These should be considered and incorporated into the basic design of studies that use structured interviews based on *DSM-III* to examine a larger number of children and adolescents from general populations.

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Twelve-Month Follow-Up of Psychotherapy for Opiate Dependence

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To provide information on the long-debated issue of the value of psychotherapy as an addition to paraprofessional counseling services for opiate addicts receiving methadone maintenance, the authors obtained 12-month follow-up data on 93 such patients randomly assigned to a 6-month course of either paraprofessional drug counseling or counseling plus professional psychotherapy. The psychotherapy patients had a significantly better overall status at 7-month follow-up and also at 12-month follow-up, 6 months after the psychotherapy ended. The authors conclude that psychotherapy can be evaluated by using scientific methods and that it can have measurable and sustained benefits in the treatment of opiate addiction.

(Am J Psychiatry 1987; 144:590–596)

In this paper we report follow-up data on a project designed to find out what benefits, if any, might result from the addition of professional psychotherapy to paraprofessional counseling services for opiate addicts receiving methadone maintenance. For this project, subjects were randomly assigned to receive either supportive-expressive psychotherapy plus drug counseling, cognitive-behavioral psychotherapy plus drug counseling, or paraprofessional drug counseling alone. Therapy was offered once a week for 24 weeks.

We have previously reported the design and rationale for this project in detail (1) as well as a range of findings from the 7-month follow-up evaluations (2–5). We found that the majority of these opiate addicts maintained on methadone had a variety of psychiatric diagnoses, primarily depression, anxiety, phobias, alcoholism, and antisocial personality (1). We also found that the three treatments were recognizably different and were consistent with the tenets specified in the manuals (2). The overall results of the 7-month follow-up revealed that although all groups showed improvements in several areas, the two groups of patients given psychotherapy in addition to drug counseling had significantly better outcomes than the patients who were randomly assigned to drug counseling alone (1).

Subsequent analysis of patient subgroups within the total sample indicated that patients with the diagnosis of antisocial personality alone had virtually no response to either psychotherapy or drug counseling, while patients with diagnoses of opiate dependence and depression showed marked improvements (3). Other analyses indicated that among patients with few or minor psychiatric symptoms the addition of professional psychotherapy was not associated with significantly more overall gains than was drug counseling alone (4). In contrast, patients with high levels of psychiatric symptoms showed little improvement with drug counseling alone but substantial gains when professional psychotherapy was added (4). Finally, our last analysis explored patient improvement as a function of therapist assignment and revealed significant differences in outcome according to which therapist treated the patient (5).

These 7-month results were valuable in that they offered a systematic and comprehensive evaluation of the benefits of professional psychotherapy. Furthermore, the results had practical implications for the treatment of opiate addicts receiving methadone maintenance. However, the 7-month evaluation occurred only 1 month after completion of the 24-week course of therapy. Thus, it was important to determine if the nature and pattern of benefits observed continued beyond this evaluation point. To address this question we now report data from these same groups obtained 12 months after intake (6 months after termination of psychotherapy).

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Supported by contract 271-81-4921 to Dr. Woody from the National Institute on Drug Abuse, Research Scientist Award MH-40710 from NIMH to Dr. Luborsky, and a VA Addiction Research Center grant to Dr. O'Brien.

The authors thank Rebecca Ashery, D.S.W., and Barry Brown, Ph.D., project officers; Beverly Pomerantz and Diane Hery for technical assistance; Jim Mintz, Ph.D., for scientific contributions; and the therapists and counselors who participated in the project.

METHOD

Since detailed descriptions of the study have been provided in earlier reports (1, 2), only a brief description of the subjects, treatments, design, and measures is furnished here.

Subjects, Treatment, and Design

The subjects were male veterans who were addicted to opiates and who were starting a new period of treatment with methadone maintenance. Patients eligible for the study were between 18 and 55 years of age, were not psychotic, and did not have a persistent organic brain syndrome. After initial screening for eligibility and provision of informed consent, patients completed an intake evaluation. They were then randomly assigned to one of three treatment conditions: drug counseling alone, counseling plus supportive-expressive psychotherapy, or counseling plus cognitive-behavioral psychotherapy. A total of 110 patients (92% of the original sample of 120) were included in the 7-month analysis. Thirty-two of these patients received supportive-expressive psychotherapy, 39 received cognitive-behavioral psychotherapy, and 39 received drug counseling alone.

Drug counseling focuses on identifying specific needs and providing support and concrete services rather than on dealing with intrapsychic processes. Counselors monitor progress by reviewing urinalysis reports for illicit drug use and employment records for vocational adjustment. They provide liaison services with physicians, courts, and social agencies. Counselors encourage patients to work toward goals specified in the treatment plan. They may also intervene directly in emergencies such as loss of a place to live, family crisis, or acute emotional disturbance. In these situations they meet with the patient, form an opinion regarding the cause of the problem, and often arrange for a meeting with the program physician, who then works toward a solution with the counselor and the patient.

Supportive-expressive psychotherapy is a psychoanalytically oriented, focal psychotherapy modeled after that described by Sifneos (6) and Malan (7). It aims to help the patient identify and work through problematic relationship themes, especially those which are related to drug dependence. The therapist identifies these themes through the relationship with the therapist (transference) and as they appear in other important relationships, such as those with the spouse or other family members. Special attention is paid to the meaning of the drug dependence and to the relationship between psychiatric symptoms and taking drugs.

Cognitive-behavioral therapy is a treatment that aims to identify and change false beliefs, unhealthy moods, and problematic behaviors. It was developed by Beck and his colleagues and has been shown to be effective for treating certain types of depression (8). Depressed patients often have false and negative beliefs, such as feeling helpless or worthless. These negative cognitions often contribute to depression, and reversing them can substantially improve the patient's mood. Similar techniques can be used to identify and alter beliefs about the need to continue using drugs.

The three treatment techniques are described in specially constructed treatment manuals. (The manual for drug counseling is available from Dr. Woody on request. The manual for supportive-expressive psychotherapy is available from Dr. Luborsky, 303 Piersol Bldg., Hospital of the University of Pennsylvania, 34th and Spruce Streets, Philadelphia, PA 19106. The manual for cognitive-behavioral psychotherapy is available from A.T. Beck, M.D., Mellon Bank Bldg., 5th Floor, 36th and Walnut Streets, Philadelphia, PA 19104.)

The manuals were used from the very start in the training as well as in the ongoing supervision of therapists and counselors. Dr. Beck and his associates supervised the cognitive-behavioral therapists, and Dr. Luborsky supervised the supportive-expressive therapists. The drug counselors were supervised by the clinic physicians, nurses, and social workers.

Measures

A series of self-report psychological tests measuring affect, cognition, and other psychiatric symptoms was administered to the patients at the start of treatment and at the 7- and 12-month evaluation points. These were the Beck Depression Inventory, the Maudsley Personality Inventory (9), the Hopkins Symptom Checklist-90 (SCL-90) (10), and the Shipley Institute of Living Scale (11). These psychological tests are well standardized, have proven reliability and validity, and were administered under supervised conditions.

A second set of measures was administered by trained independent raters. These included the Lifetime and Change versions of the Schedule for Affective Disorders and Schizophrenia—the SADS-L (12) and the SADS-C (13). These are structured interviews that were administered at the start of treatment by a trained physician or psychologist and then used to derive *DSM-III* and Research Diagnostic Criteria (RDC) (14) diagnoses. The SADS-C was repeated at the follow-up evaluation points. In addition, the Addiction Severity Index interview (15) was administered to all patients at the start of treatment and again at the 7- and 12-month evaluation points. The Addiction Severity Index is a structured clinical/research interview designed to assess the severity of problems in several areas of functioning commonly impaired in drug-dependent patients: medical, employment or support, drug use, alcohol use, legal, and psychiatric. In each of these areas, questions are asked to measure the number, extent, and duration of problem symptoms in the patient's lifetime and in the past 30 days. Sets of objective and subjective items from each of the problem areas are standardized and summed to produce composite or factor scores that provide reliable, valid general measures of problem severity in each area.

All follow-up evaluations were done by trained and experienced research technicians who had had no role in the treatment. All follow-up evaluations were done in person or over the telephone within 2 weeks of the 12-month anniversary date. Twenty-eight (88%) of the original 32 supportive-expressive psychotherapy patients were contacted for follow-up at 12 months, compared with 34 (87%) of the 39 cognitive-behavioral psychotherapy patients and 31 (79%) of the drug counseling patients. There were no significant differences between groups in the proportion of subjects contacted at 12 months according to chi-square analysis.

RESULTS

The results of the 12-month follow-up evaluation are presented in three parts. In part one, all subjects who received a 12-month follow-up were considered. Their performance was evaluated within groups by comparing pretreatment to follow-up status and between groups by comparing the 12-month status of the three treatment groups, adjusted for pretreatment differences. In part two, all subjects who received both a 7-month and a 12-month follow-up were considered. Analyses similar to those described in part one were carried out, providing an opportunity to evaluate patient change at three evaluation points. In part three, additional data were considered for the smaller group of subjects who remained on methadone maintenance throughout the year following the study. The standard program measures of during-treatment adjustment are presented for this self-selected subgroup.

Baseline to 12-Month Changes

Addiction Severity Index interviews and a battery of psychological tests were completed on 93 subjects at the start of the project and at the 12-month follow-up. Factor scores from the Addiction Severity Index, single items from this index, and the psychological test results are presented for all three treatment groups at both evaluation points in table 1. Within-group comparisons were made by using paired t tests, and 12-month status comparisons across groups were made by using the analysis of covariance procedure, with the pretreatment criterion score as the covariate. These between-group analysis of covariance results are presented in the last column of table 1.

In general, the results of these comparisons between start of treatment and 12-month follow-up with 93 patients parallel our earlier findings with 110 subjects at the 7-month follow-up. Most measures of patient status showed improvement at 12 months across all groups. However, the two psychotherapy groups showed more improvements at a higher level of significance than the drug counseling group.

Patients in the supportive-expressive psychotherapy group showed improvement on 15 of 22 measures; improvement on 10 of these was significant (table 1). The major changes seen were in the areas of psychiatric symptoms and employment or support, although drug use and illegal activity showed positive change. One measure that showed worsening was the medical condition of the patients: a slight increase in the medical factor score and a significant increase in the number of days of reported medical problems were seen.

Patients in the cognitive-behavioral psychotherapy group showed improvements on 20 of 22 criteria; 12 of these reached statistical significance (table 1). The major improvements in this group were in measures of alcohol and drug use, illegal activity, and psychiatric symptoms. There was some evidence of improvement in employment status and no change in medical condition.

Patients in the drug counseling group showed improvements on 11 of the 22 measures; two of these reached statistical significance, and two additional measures showed a trend toward significant improvement (table 1). The only area to show major change was drug use. In contrast, the area of legal status showed a trend toward worsening.

Results of these within-groups comparisons suggested that the two psychotherapy groups showed better performance than the drug counseling group. In a further examination of this possibility, we performed analyses of covariance on the 12-month scores, adjusting for differences in pretreatment criterion scores. As can be seen in the last column of table 1, 11 of the 22 comparisons showed a significant between-groups effect. In no case did the drug counseling group show a better adjusted outcome score than the psychotherapy groups, thus supporting the results of the within-group analyses. There was no evidence from either the within-group analyses or the results of the analysis of covariance for differential effectiveness between the two psychotherapy groups.

Baseline to 7-Month to 12-Month Changes

As an additional indication of the nature of changes in patients across the three evaluation periods of the project, we examined the baseline to 7-month to 12-month changes in 84 patients who completed all three evaluations. The same statistical tests that had been used in the part one analyses were repeated for this examination. The results are presented for all three groups at each evaluation point in table 2, and all statistical comparisons were evaluated against the baseline values.

As can be seen in table 2, the majority of significant improvements shown by the supportive-expressive psychotherapy subjects at the 7-month evaluation remained evident at 12 months. In fact, there was evidence for continued improvement in the areas of employment, legal status, and psychiatric condition.

Similar results were also seen for patients in the cognitive-behavioral psychotherapy group. Again, the

TABLE 1. Social and Psychiatric Measures at Baseline and 12-Month Follow-Up for 93 Patients Receiving Methadone Maintenance Who Were Given Counseling or Counseling Plus Psychotherapy for 6 Months

Measure[a]	Supportive-Expressive Psychotherapy Plus Drug Counseling (SE) (N=28)				Cognitive-Behavioral Psychotherapy Plus Drug Counseling (CB) (N=34)				Drug Counseling Alone (DC) (N=31)				Significant Differences Between Groups at 12 Months[b]
	Baseline		12 Months		Baseline		12 Months		Baseline		Months		
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Addiction Severity Index variables													
Medical factor score	183	21	188	16	286	27	268	31	334	34	369	32	
Days with medical problems	2	1	7[c]	2	6	3	9	3	8	3	11	3	
Employment factor score	305	102	191[d]	87	311	88	185[c]	51	241	106	163	101	
Days working	8	3	16[d]	4	7	4	10	4	12	2	12	2	(SE+CB)>DC[c]
Money earned ($)	301	141	805[c]	126	519	108	495	131	568	111	486	88	SE>(CB+DC)[c]
Alcohol use factor score	74	11	64	12	101	11	59[c]	7	86	12	103	14	
Days drinking	8	2	7	2	7	2	5	2	8	2	8	2	
Days drunk	1	1	1	1	3	1	1[c]	1	2	1	2	1	
Drug use factor score	167	8	151[c]	11	196	14	101[d]	11	219	21	127[d]	16	
Days using opiates	4	2	2	2	9	2	2[d]	1	8	2	1[d]	1	
Days using stimulants	2	1	3	1	1	1	0	1	2	1	1	1	
Days using depressants	2	1	3	1	1	1	0	1	2	1	1	1	
Legal factor score	219	60	117[d]	41	217	49	106[d]	21	81	20	142[e]	20	
Days committing crimes	5	1	3	2	7	2	2[c]	1	2	2	4	2	DC>SE>CB[c]
Illegal income ($)	102	88	140	71	201	80	60[d]	29	159	61	177	75	(DC+SE)>CB[c]
Psychiatric factor score	171	38	80[d]	19	156	44	75[d]	20	160	26	111[f]	31	DC>(SE=CB)[d]
Beck Depression Inventory score	15	3	9[c]	2	14	2	9[c]	2	14	3	11	3	DC>(SE=CB)[d]
Maudsley neuroticism score	26	4	19[c]	2	26	4	21	4	28	4	26	4	DC>(DC=SE)[c]
SADS													
Anxiety score	18	3	18	4	20	4	17	3	18	3	22	4	DC>(DC=SE)[c]
Depression score	20	5	16	4	23	5	20	5	21	4	20	2	(CB=DC)>SE[c]
SCL-90 score	66	10	29[d]	5	56	7	47[c]	4	72	12	54[g]	11	DC>CB>SE[d]
GAS score (SADS-C)	66	7	78[c]	7	57	8	69[d]	6	66	9	68	8	DC>CB>SE[d]

[a]All criteria were measured during the 30-day period preceding the start of the study and at the 12-month evaluation. Higher factor scores indicate greater problem severity.
[b]Analysis of covariance was performed on 12-month scores by using the baseline values as the covariate.
[c]$p<.05$.
[d]$p<.01$.
[e]$p<.09$.
[f]$p<.07$.
[g]$p<.08$.

majority of gains shown at the 7-month point were evident at 12 months, and additional improvement was seen in drug and alcohol use and psychiatric status.

More mixed results were seen in the data for the drug counseling patients. Although the gains in employment and drug use seen at 7 months were continued at 12 months, there was evidence for attrition of some psychiatric improvements. In fact, in the legal area, there was evidence for worsened status in comparison with baseline evaluation.

The impressions conveyed by these within-group comparisons were supported by the results of analyses of covariance on the 12-month data, using the baseline score as the covariate in each analysis. Twelve of the 22 analyses indicated a significant between-groups effect on the adjusted 12-month outcome (table 2). In every case, the drug counseling group showed significantly poorer outcomes than the psychotherapy groups. As in the part one analyses, there was no evidence for a significant difference in performance between the two psychotherapy groups.

During-Treatment Measures

Although the analyses described in parts one and two considered all subjects, whether they remained in the methadone program or not, some patients from each of the three groups did remain in the methadone program throughout the 12 months following the study. Obviously, these subsamples were self-selected and not representative of the total group. However, the fact that they were still in methadone maintenance treatment enabled us to look at our ongoing clinic records for out most objective measures of performance (methadone dose, prescriptions for ancillary psychotropic medication, and urinalysis results), and we felt that these observations provided additional information regarding the maintenance of treatment benefits.

TABLE 2. Social and Psychiatric Measures at Baseline, 7-Month Follow-Up, and 12-Month Follow-Up for 84 Patients Receiving Methadone Maintenance Who Were Given Counseling or Counseling Plus Psychotherapy for 6 Months

	Supportive-Expressive Psychotherapy Plus Drug Counseling (SE) (N=25)						Cognitive-Behavioral Psychotherapy Plus Drug Counseling (CB) (N=31)					
	Baseline		7 Months		12 Months		Baseline		7 Months		12 Months	
Measure[a]	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Addiction Severity Index variables												
Medical factor score	218	27	209	30	181	31	309	31	281	31	262	26
Days with medical problems	2	2	3	2	2	2	7	2	9	2	6	3
Employment factor score	312	24	261[c]	20	204[d]	21	306	26	204[c]	27	186[c]	19
Days working	8	2	13[c]	2	15[d]	2	7	1	8	1	9	2
Money earned ($)	289	102	514[c]	111	605[c]	201	311	141	391	146	488	202
Alcohol use factor score	73	11	76	13	62	18	106	19	60[c]	8	58[c]	6
Days drinking	8	2	8	2	6	1	8	2	6	2	5	2
Days drunk	1	1	2	1	1	1	2	1	1	1	1	1
Drug use factor score	177	21	145[c]	16	158	17	204	18	121[c]	8	96[d]	11
Days using opiates	5	1	2[c]	1	3	2	9	2	6[c]	2	2[c]	2
Days using stimulants	2	1	1	1	3	1	2	1	1	1	0[c]	1
Days using depressants	4	2	4	2	3	2	3	1	1[c]	1	1[c]	2
Legal factor score	229	27	121[d]	19	125[d]	13	199	26	88[d]	12	93[d]	16
Days committing crimes	5	2	3	1	3	2	6	2	1[c]	1	2[c]	2
Illegal income ($)	108	56	104[c]	31	59[d]	19	177	31	53[d]	13	54[d]	13
Psychiatric factor score	167	30	74[d]	16	70[d]	12	158	26	79[d]	19	69[d]	14
Beck Depression Inventory score	14	2	8[d]	2	9[d]	2	14	3	10[c]	2	9[c]	1
Maudsley neuroticism score	26	4	22	6	19[c]	2	26	4	24	4	20[c]	2
SADS												
Anxiety score	18	3	17	3	18	3	20	3	19	3	17	3
Depression score	20	4	17	3	17	3	23	3	21	4	20	4
SCL-90 score	64	9	37[d]	7	30[d]	6	58	6	50	6	43[c]	5
GAS score (SADS-C)	63	9	77[c]	7	81[d]	9	60	7	69[c]	7	79[d]	8

[a]All criteria were measured during the 30-day period preceding the start of the study and at the 12-month evaluation. Higher factor scores indicate greater problem severity.
[b]Analysis of covariance was performed on 12-month scores by using the baseline values as the covariate.
[c]$p<.05$.
[d]$p<.01$.

Fourteen of the supportive-expressive psychotherapy patients were on methadone at the time of the 12-month evaluation, compared with 24 cognitive-behavioral psychotherapy patients and 24 drug counseling patients. The mean±SD methadone doses for these three groups were 36±8 mg for the supportive-expressive psychotherapy group, 42±12 mg for the cognitive-behavioral psychotherapy group, and 5±18 for the drug counseling group. Two of the supportive-expressive psychotherapy patients were prescribed an ancillary psychotropic medication for sleep, anxiety, or depression by one of our three program physicians. This compared with three of the cognitive-behavioral psychotherapy patients and 11 of the drug counseling patients who were prescribed medication. Urinalysis results for the week of the 12-month evaluation revealed that two of the supportive-expressive psychotherapy patients had a positive assay for at least one of the drugs tested, while three cognitive-behavioral psychotherapy patients and three of the drug counseling

Drug Counseling Alone (DC) (N=31)						Significant Differences Between Groups at 12 Months[b]
Baseline		7 Months		12 Months		
Mean	SD	Mean	SD	Mean	SD	
331	26	360	26	384	30	DC>(SE=CB)[c]
7	2	8	2	11	2	DC>(SE=CB)[d]
194	11	186[c]	8	163[c]	8	(DC=CB)>SE[c]
11	2	13	2	12	3	
541	216	407	161	423	173	DC<(SE=CB)[c]
90	11	80	9	85	8	DC>SE>CB[c]
8	1	7	1	7	2	
2	1	1	1	2	2	
205	12	112[d]	13	116[d]	12	
8	1	2[c]	2	2[c]	1	
1	1	1	1	2	1	
3	2	2	1	4	2	DC>SE>CB[c]
86	11	106	14	150[c]	15	DC>(SE=CB)[d]
2	1	3	1	4	2	DC>(SE=CB)[c]
160	19	188	41	178	46	DC>(SE=CB)[c]
162	36	106[c]	29	123	27	DC>(SE=CB)[d]
15	3	10[c]	2	12	2	
29	4	25[c]	3	27	5	DC>(SE=CB)[c]
19	3	21	3	23	3	
22	4	20	3	21	3	
70	7	58	7	57	7	
61	9	66	9	69	9	DC<CB<SE[c]

patients had positive assays, indicating some illicit drug use.

Although these subsamples are too self-selected and incomplete to compare statistically, the pattern of results suggests that the psychotherapy groups required lower doses of methadone and had less need for psychotropic medications than the drug counseling group while maintaining comparably low levels of illicit drug use. We feel it is noteworthy that this is exactly the same pattern of results that was seen during the actual study with complete samples (1, 4). We had already evaluated outcome in the total population of study patients, but we felt that these data would provide additional (albeit suggestive) evidence for the continuation of benefits from psychotherapy even among the subsample of patients who remained in methadone treatment.

DISCUSSION

The results from our analysis of baseline to 12-month follow-up were similar to those previously reported for 7-month analyses (1). All treatment groups showed improvements. However, the two psychotherapy groups showed more improvements than the drug counseling group over a wider range of outcome measures, with marked changes in the areas of employment, legal status, and psychiatric symptoms and with less use of psychotropic medications. The results of our part two analyses indicated that among those patients who had received baseline, 7-month, and 12-month evaluations, the two psychotherapy groups showed sustained improvements at 12-month follow-up and indications of continued improvement over the 7-month levels in the areas of employment, drug and alcohol use, and psychiatric status. The two psychotherapy groups did not differ significantly in number or magnitude of improvements shown. In contrast, the drug counseling patients showed maintenance of some improvements across the two follow-up points (particularly drug use and employment) but clear attrition of some gains at the 12-month point (particularly in illegal activity). These results indicate that the gains measured in the psychotherapy patients at 7 months were maintained at 12 months despite the absence of ongoing additional psychotherapy.

Although the combined data indicate substantial improvement, they do not indicate that the drug addiction was "cured" by psychological treatments, if the term "cured" is defined as the complete cessation of all drug use. However, it is important to note that improvements in areas such as drug use, employment, legal status, and psychiatric status are meaningful in economic and social terms, not only to the patient but to the patient's family, employer, and the community.

This study aimed to identify the possible contribution that psychotherapy might offer to opiate addicts receiving methadone maintenance; therefore, it is called a psychotherapy study. In reality, however, it is a psychotherapy/psychopharmacology study. Psychotherapy with these patients would not have been possible without the stabilizing effects of methadone. However, continued participation in psychotherapy was associated with the reduced use of all drugs (prescribed and illicit), while also providing additional benefits.

These results are consistent with the trend seen in earlier psychotherapy research with drug-dependent patients (16–22) and with a more recent controlled

study (23) done as part of another project in our clinic setting. Although we deal with a different type of problem, our findings are similar to those of Falloon et al. (24), who found that a specific type of family therapy, when combined with pharmacotherapy, reduced the incidence of relapse and the length of hospital stay in schizophrenic patients whose families had high expressed emotion and also resulted in less use of psychotropic medication. These studies, taken together, suggest that psychological treatments can provide significant additional benefits for conditions that have biological components usually requiring pharmacotherapy.

We conclude that this study and our more recent work (23) demonstrate that psychotherapy can have measurable and sustained benefits in the treatment of opiate addiction within our own clinic setting. We are currently studying its effectiveness in several nearby community-based clinics to see what results occur when we attempt to implement similar procedures in other treatment settings.

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Adrenocortical Function and Depressive Illness in Mentally Retarded Patients

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The authors administered a 1-mg dexamethasone suppression test (DST) to 85 institutionalized adults with mild to profound mental retardation after screening to exclude false-positive nonsuppression. Thirty-one (36%) of these subjects had baseline hypercortisolemia, which was significantly correlated with age, symptoms, and "modified" DSM-III *criteria for major depressive disorder. Twenty (24%) of the 85 subjects were nonsuppressors (5 μg/dl) after testing; nonsuppression was significantly related to age, female sex, level of retardation, symptoms, and "modified"* DSM-III *criteria for major depressive disorder (sensitivity 41%, specificity 81%). First-order partial correlations maintained significant relationships between age and severity of retardation but not sex. Mental retardation itself did not appear to invalidate the DST.*

(Am J Psychiatry 1987; 144:597–602)

The simultaneous occurrence of affective disorders and mental retardation is well recognized (1, 2). Reid (3) reported that depression and mania could be clinically diagnosed in borderline-to-mildly-retarded subjects but that the diagnosis of severely retarded subjects required long-term observation of behavior and sleep/wake patterns. Rivinus and Harmatz (4) concurred, and Matson and Barrett (5) indicated that diagnostic systems for affective disorders in nonretarded patients may not be useful in retarded persons. Sovner and Hurley (6) agreed that intellectual and social impairments of retarded individuals greatly influence their clinical presentation. Clearly, the diagnosis of depressive illness in retarded persons presents special challenges.

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The authors thank the staff at Glenwood State Hospital-School, Glenwood, Iowa, and Debra Ruedrich for their cooperation on this project and Cynthia Wilmoth and Trina Carroll for preparation of the manuscript.

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In nonretarded persons, it is known that baseline hypercortisolemia and escape from cortisol suppression on testing with dexamethasone occur in a substantial number of depressed patients (7, 8). Carroll et al. (8) reported nonsuppression in approximately 50% of endogenously depressed patients, with a "specificity" of 96%. Others have disputed both figures, noting abnormal dexamethasone suppression test (DST) results in patients with mixed bipolar disorder (9), schizophrenia (10), alcoholism (11), dementia (10, 12), and as a function of advancing age (13, 14). However, in most studies neither age, sex, severity of symptoms, nor use of tricyclic antidepressants, lithium, antipsychotics, or benzodiazepines appeared to result in false-positive DST results.

Finally, there have been no major reports that level of intelligence affects the DST. Little literature addresses hypothalamic-pituitary-adrenal (HPA) axis function in retarded persons; most is anecdotal or reports adrenal hypofunction. In an important study, Beckwith et al. (15) administered DSTs to 57 institutionalized retarded subjects who scored either high or low on a depressive symptom checklist. They concluded that the DST is valid in retarded depressive subjects, but they did not report the effect of retardation or other factors on nonsuppression. Toward this end, we conducted a pilot study using the DST independently in eight institutionalized retarded adults after screening to exclude subjects with false-positive nonsuppression (16). Three of the eight subjects revealed nonsuppression: two had a cortisol level greater than 5 μg/dl, and one, 4 μg/dl. Two of these three subjects also had behavioral disturbances (difficulty sleeping, isolation, loss of appetite, and self-abuse) that might be attributed to a depressive disorder. Subsequently, the study was expanded to systematically evaluate HPA axis function in persons with mental retardation, using the DST independently to identify endogenous depression.

METHOD

The subjects were selected from all adult residents of a large hospital-school for the mentally retarded. Subjects with any of the following were excluded: preg-

nancy, Cushing's or Addison's disease, weight less than 80% of ideal or loss of more than 20 lb in the index period, major traumatic or physical illness during the index period, diabetes, alcohol use, or seizure disorder. (The index period included the 6 months before and 1 month after DST administration.) Also excluded were subjects receiving phenytoin, carbamazepine, barbiturates, meprobamate, methaqualone, glutethimide, methyprylon, reserpine, corticosteroids, estrogen, or birth control pills (17). Subjects taking benzodiazepine and nonbenzodiazepine hypnotic/anxiolytics were included if their doses were below the equivalent of 25 mg/day of diazepam, as were subjects taking antidepressants, antipsychotics, antiparkinsonians, antihistamines, and lithium. An attempt was made to select 100 subjects equally divided by sex and by level of retardation; however, most of the mild-to-moderately retarded women were taking birth control pills and therefore were excluded. Informed consent for participation was obtained from guardians for the 85 subjects who entered the study.

Data Collection

The medical and pharmacy records of all 85 subjects were reviewed by raters blind to cortisol results. Charts were examined for demographic data, severity of mental retardation, family history of psychiatric illness, and evidence of medical and psychiatric illnesses in the 2 months preceding and 1 month following administration of the DST. A dichotomous (present versus absent) symptom checklist included the *DSM-III* criteria for major depressive disorder and other behaviors that often initiate psychiatric consultation in retarded persons (17). Checklist symptoms included dysphoria, delusions, auditory and visual hallucinations, and decreased or increased appetite, weight, energy, and motor and verbal activity. Other symptoms were initial, middle, and terminal insomnia; decreased interest, concentration, attention span, and hygiene; public masturbation; running away from the hospital-school; inappropriate undressing; withdrawal; self-reproach; anxiety; and somatic complaints. The list continued with crying, laughing, suicidal talk, aggression toward persons or property, incontinence, stereotypy, and posturing.

For the index period, data were collected from both physician and nursing progress notes, which were required weekly or as clinically indicated. To corroborate the medical records, hospital staff were then interviewed by psychiatric raters who were blind to DST results. Standard psychiatric examination of subjects proved unsatisfactory, especially with the severely retarded subjects. The focus of our psychiatric examination was restricted to data from the medical record and staff observations, an approach supported by Shapiro and Barrett (18).

The DST protocol was that standardized by Carroll et al. (8). Subjects underwent phlebotomy at 8:00 a.m., 4:00 p.m., and midnight on 2 consecutive days, with administration of dexamethasone, 1 mg orally, at 11:00 p.m. on day 1. Plasma cortisol level was measured by radioimmunoassay (high split-sample agreement) using the Cortisol RIA Kit and instructions supplied by Amersham Corporation (Arlington Heights, Ill.). We took note of any individuals demonstrating resistance to phlebotomy.

Statistical Analysis

Coded data were statistically analyzed by using the SPSS^x program (19). Day 1 cortisol ranges (determined by Amersham Corporation) were 7–27 μg/dl at 8:00 a.m. and 2–10 μg/dl at 4:00 p.m. and midnight. Postdexamethasone cortisol levels were dichotomized on the basis of suppression (less than 5 μg/dl) and escape from suppression (5 μg/dl or more); data were also analyzed on the basis of cutoffs of 4 and 6 μg/dl. Symptoms were counted, and specific symptoms were compared with *DSM-III* criteria for major depressive disorder as well as "modified" criteria for major depressive disorder that eliminated the requirement for dysphoria (based on the inability of many retarded persons to report their mood) and added "crying spells" to the associated symptoms. Time criteria for *DSM-III* were met.

Pearson product-moment correlation coefficients (r) were computed between two quantifiable variables. The relationship between two dichotomous variables was analyzed with phi coefficients (ϕ) with chi-square to measure statistical significance. The relationship between a dichotomous variable and a quantitative variable was analyzed by point-biserial correlation coefficient. Partial correlations were computed to control for multiple variable effects.

RESULTS

Description

The 85 subjects were 53 men and 32 women; their age range was 18–63 years (mean=32.5 years). Mean length of hospitalization was 16.3 years (range 0–47 years). The subjects' mean IQ was 35.3 (range, 10–85), reflecting more severe-to-profound mental retardation in the sample. One subject (1%) had borderline combined with mild, seven (8%) had mild, 27 (32%) had moderate, 25 (29%) had severe, and 25 had profound mental retardation. Fifteen (18%) of the subjects had a family history of psychiatric illness, and 11 (13%) of them had a family history of mental retardation. Nine (11%) of the subjects had recorded psychiatric diagnoses during the index period (five unspecified, one attention deficit disorder with hyperactivity, two bipolar disorder, and one generalized anxiety disorder). The number of signs or symptoms ranged from 0 to 12 (mean=1.89). Forty-four (52%) of the subjects had at least one symptom or sign; the mean number among those with any was 3.64. Four-

TABLE 1. Correlation of Sociodemographic and Clinical Characteristics With Cortisol Nonsuppression in 85 Mentally Retarded Adults Given the DST

	Plasma Cortisol Level (μg/dl)					
	≥4.0 (N=23)		≥5.0 (N=20)		≥6.0 (N=16)	
Characteristic	Correlation	p	Correlation	p	Correlation	p
Age (years)[a]	.3086	.01	.3248	.001	.2994	.01
Hospitalization (years)[a]	.1626	n.s.	.1384	n.s.	.1320	n.s.
Extent of mental retardation[a]	.2964	.01	.2637	.01	.1979	.05
Sex[b]	.1280	n.s.	.1987	n.s.	.1849	n.s.
Any psychiatric diagnosis[b]	.1347	n.s.	.1697	n.s.	.2256	.05
Number of signs or symptoms[a]	.2966	.01	.2617	.01	.2911	.01
Resistance to phlebotomy[b]	.1277	n.s.	.1715	n.s.	.1327	n.s.
Elevated baseline cortisol level[b]	.1437	n.s.	.1559	n.s.	.2604	.02
Number of medications[a]	.2085	.05	.2110	.05	.2435	.02
Treatment with anxiolytics[b]	.0802	n.s.	.0969	n.s.	.1238	n.s.
Treatment with hypnotics[b]	.2457	.05	.2803	.01	.3373	.01
Etiology of mental retardation						
Unknown[b]	.1110	n.s.	.1469	n.s.	.1637	n.s.
Genetic[b]	−.0223	n.s.	−.0543	n.s.	−.0009	n.s.
Perinatal[b]	−.0563	n.s.	−.0220	n.s.	.0296	n.s.
Trauma-birth complications[b]	.0758	n.s.	.1062	n.s.	.0509	n.s.
Social-environmental deprivation[b]	.2457	.05	.2803	.01	.2198	.05

[a]Point-biserial correlation.
[b]Phi coefficient and chi-square probability.

teen (16%) of the subjects were resistant to phlebotomy. Thirty-one (36%) had at least one elevated baseline cortisol level, and six (7%) had two. *ICD-9* codes for etiology of mental retardation were unknown, N=41 (48%); genetic, N=16 (19%); perinatal, N=14 (17%); trauma-birth complications, N=8, (9%); and social-environmental deprivation, N=6 (7%).

Forty-two (49%) of the patients were receiving medications during the index period. These 42 patients received 76 medications; 36 (49%) of these medications were antipsychotics. The number of medications received per subject ranged from 0 to 5; the mean number of medications taken per subject was 0.89.

Twenty (24%) of the 85 subjects demonstrated escape from cortisol suppression on at least one sample. Of these, seven (35%) had two values above 5 μg/dl, and one (5%) had all three. The 4:00 p.m. sampling time identified 80% of nonsuppressors; only four (20%) revealed nonsuppression only at 8:00 a.m. or midnight.

Analysis

Age, sex, and level of mental retardation were not significantly related to hospitalization, family history, diagnosis, or number of medications. However, individuals with mild-to-moderate mental retardation were more likely to be taking antidepressants (point-biserial correlation=−.2209, N=85, p≤.05) and less likely to be taking anxiolytics than more retarded subjects (point-biserial correlation=.1937, N=85, p≤.05). Older age was correlated with anxiolytic use (point-biserial correlation=.3982, N=85, p≤.001). More symptoms were significantly related to both greater age (r=.1793, N=85, p≤.05) and greater retardation (r=.3021, N=85, p≤.01). Resistance to phlebotomy was unrelated to any variable; only one resistant subject was DST positive. Baseline hypercortisolemia was significantly correlated with both age (point-biserial correlation=.3505, N=85, p≤.001) and number of symptoms (point-biserial correlation=.2523, N=85, p≤.01) but not DST nonsuppression.

Several variables were significantly correlated with DST nonsuppression (cortisol level of 5 μg/dl or more), including severity of mental retardation, greater age, more symptoms, number of medications, treatment with hypnotics, and social-environmental deprivation as mental retardation etiology (table 1).

In examining sign and symptom data obtained by using "modified" *DSM-III* criteria for major depressive disorder, we found that only three (4%) of the 85 subjects met requirements for four symptoms; however, 17 (20%) met requirements for three symptoms. This variable was significantly correlated with baseline hypercortisolemia (ϕ=.2933, p=.01), and seven (41%) of these 17 subjects also revealed DST nonsuppression at 5 μg/dl (ϕ=.2080, p=.055) (sensitivity, true-positive), nine (53%) at 4 μg/dl (ϕ=.2913, p=.007), and six (35%) at 6 μg/dl (ϕ=.2107, p=.052). The specificity (true-negative) was 81% at 5 μg/dl, 79% at 4 μg/dl, and 85% at 6 μg/dl.

Fourteen (32%) of 44 patients with signs or symptoms demonstrated DST nonsuppression, and eight individual signs or symptoms (visual hallucinations, initial and middle insomnia, decreased activity, crying, laughing, aggression toward staff, and undressing)

were significantly related to positive DST results. At 4 μg/dl, three other signs or symptoms (appetite change, terminal insomnia, and verbalization) were also significant. These 11 symptoms constituted a "depressive syndrome," which was also significantly correlated with baseline hypercortisolemia (ϕ=.2176, p=.05).

Next, for each variable significantly related to DST nonsuppression, "modified" *DSM-III* criteria for major depressive disorder, or "depressive syndrome," we reanalyzed the data using partial correlations. Controlling for age removed the previously significant relationship between DST nonsuppression and number of medications. Controlling for extent of mental retardation changed no significant correlations. Controlling for use of hypnotic medication eliminated the significant relationship between nonsuppression and number of medications. Controlling for baseline hypercortisolemia eliminated the significant relationship between DST nonsuppression at 5 and 6 μg/dl and "modified" *DSM-III* criteria for major depressive disorder; the relationship remained significant at 4 μg/dl (r=.2633, p≤.01) and approached significance at 5 μg/dl (r=.1719, p=.059) and 6 μg/dl (r=.1455, p=.093). Third-order partial correlation analysis controlling for combinations of three of the four variables (age, level of mental retardation, elevated baseline cortisol level, and use of hypnotics) changed no significant relationships.

Finally, we reanalyzed our data eliminating the six patients receiving hypnotics. Reanalysis of the 79 remaining subjects eliminated previous relationships between lower IQ and anxiolytic use and between greater age and more symptoms. Four of the six subjects receiving hypnotics were DST nonsuppressors; their elimination left 16 (20%) nonsuppressors in a total sample of 79 subjects. The number of medications was no longer related to DST nonsuppression; all other relationships remained or approached significance.

DISCUSSION

We found few significant demographic relationships. Greater mental retardation was related to female sex (mildly retarded women taking birth control pills were excluded), which probably represents sample bias. Symptoms and use of anxiolytics correlating with greater age and greater mental retardation may reflect frequent symptomatic illnesses, true anxiety symptoms, or nonspecific anxiolytic treatment of behavioral disorders in older, more retarded individuals. Antidepressant use correlating with higher IQ may reflect validity of clinical presentation of depressive disorders or increased self-reporting in these patients. However, most data on medication involved small numbers of patients; significant correlations may represent practice or other clinical artifacts.

As noted, baseline hypercortisolemia was common (31 [36%] of the subjects) and correlated with both greater age and more symptoms. Regarding age, Stokes et al. (13) reported baseline hypercortisolemia and Davis et al. (14) reported hypercortisolemia and abnormal DST results in older depressed patients compared with younger counterparts, but both groups of researchers agreed that HPA axis function appears unaffected by advancing age in healthy subjects. In our sample, the significant correlation between "modified" *DSM-III* criteria for major depressive disorder and baseline hypercortisolemia supports a similar relationship among age, depressive symptoms, and elevated baseline cortisol in mentally retarded individuals.

The fact that 20 (24%) of a prescreened sample of 85 institutionalized retarded adults exhibited nonsuppression is of interest. Except for Beckwith et al. (15) and Sandman et al. (20), psychiatric work with the DST has focused on symptomatic nonretarded adults or normal subjects. Amsterdam et al. (21) reported nonsuppression in 15% of healthy outpatients; Stokes et al. (13%) found a 10% false-positive rate in 77 normal adults, a rate more than doubled in our sample. Possible explanations might include factors correlated with nonsuppression in our sample (greater age, greater mental retardation, use of hypnotics, more symptoms) or the institutionalization itself.

Age and DST nonsuppression has been discussed. As for IQ, one report on nondepressed retarded subjects (22) noted adrenal hypofunction; another (23) reported correlations between urinary free cortisol and cognitive dysfunction in nonretarded depressed patients. Others (12, 24) have disputed finding DST nonsuppression in advanced dementia *without* depression. Beckwith et al. (15) found a high rate of false-positive nonsuppression (29%) in apparently nondepressed mentally retarded adults. They ascribed this finding to either early administration of dexamethasone in their protocol or missed "diagnoses" of the "withdrawn" depressed retarded patient. An alternate explanation would be some effect of mental retardation itself in producing baseline hypercortisolemia and early escape from cortisol suppression. In our sample, six (30%) of 20 nonsuppressors were asymptomatic on chart review. However, controlling for the extent of mental retardation did not alter significant relationships between DST nonsuppression and symptoms; it would seem that mental retardation is not a technical exclusion for the DST and that the DST is clinically valid in retarded subjects.

Another possible source of nonsuppression could be some effect of institutionalization. Cortisol hypersecretion can occur with novel stressors (surgery, vigorous exercise), but chronic stress is thought to produce habituation of cortisol response in both animals and humans (25). Sandman et al. (20) found that most of those depressed retarded subjects who were hospitalized longest manifested normal suppression; they speculated a physiological breakdown of the HPA axis in these subjects. Another explanation would be the habituation of cortisol response to the chronic stress of institutional living. Our sample produced no signifi-

cant relationship between length of hospitalization and either baseline hypercortisolemia (r=.1061, p=.160) or DST nonsuppression (r=.1384, p=.099).

Several authors have reported false-positive nonsuppression with certain drugs, but no significant effect from most psychotropics (tricyclic antidepressants, monoamine oxidase inhibitors, lithium, antipsychotics, or low-dose benzodiazepines). The significant correlation between early escape from cortisol suppression and use of hypnotics in our sample may reflect enzyme induction with false-positive nonsuppression or nonspecific pharmacological approaches to patient management. Some antipsychotics were used empirically (nine of the patients had psychiatric diagnoses, but 31 [37%] received antipsychotics), but antipsychotic use was not correlated with nonsuppression; similar nonspecific use of hypnotics does not explain the hypnotic-nonsuppression correlation. Removal of the subjects treated with hypnotics from analysis produced no major change; hypnotic use is not a sufficient explanation for the HPA axis activation seen.

A final explanation for the baseline hypercortisolemia and DST nonsuppression observed could be that symptomatic individuals had an undiagnosed psychiatric disorder, major depressive disorder, reflected in HPA axis activation but unapparent because of their retardation. The difficulty in diagnosis of affective disorder in patients with substantial mental retardation has been discussed in this paper and by others (*5*, *6*). When we retrospectively diagnosed our sample using standard and "modified" *DSM-III* criteria for major depressive disorder, no patient had a chart diagnosis of major depressive disorder and only three (4%) met "modified" criteria requiring four symptoms, but 17 (20%) had three symptoms. Seven (41%) of these 17 subjects were DST nonsuppressors, producing a sensitivity similar to that reported for nonretarded depressed subjects. Our checklist method, likely to result in underreporting, makes significant correlations between nonsuppressor status and symptoms appear more striking. The substantially lower specificity (81%) is perhaps attributable to the intervening variables already noted.

Finally, DST escape was used independently to identify clinical measures that separated nonsuppressors from suppressors, irrespective of psychiatric diagnosis. Using a similar method, Reus (26) found nonsuppressors to have more symptoms, such as sleep and attention difficulties, anxiety, and anergy. Interestingly, five of our 11 nonsuppressor-associated symptoms correspond with Reus's symptoms and are found in major depressive disorder. Two others are found in other affective disorders, notably, crying spells in dysthymic disorder and laughter in bipolar states. Aggression toward staff, verbalization, and undressing may reflect psychomotor agitation and be behavioral manifestations of affective disorder in mental retardation. Visual hallucinations do not specifically appear in nonretarded nonpsychotic major depressive disorder, but they have been described (27) in both manic and depressed retarded individuals and have been noted (6) as a specific symptom produced by affective disorder in mental retardation. Thus, our nonsuppressor patients were different from their suppressor counterparts in some traditional depressive symptoms (crying and sleep, appetite, and activity changes), some that may represent the overlay of intellectual and social retardation on symptom form (physical aggression, verbalization, undressing), and one that may be rather unique in depressed retarded individuals (visual hallucinations).

Clinical recommendations based on these findings must be viewed as preliminary. As noted elsewhere, our data support the inclusion of major depressive disorder and other affective disorders in the differential diagnosis of mentally retarded individuals with symptoms of sleep, appetite, and psychomotor disturbance; crying; laughing; aggression; or visual hallucinations. In those with severe-to-profound mental retardation, for whom self-reporting of symptoms is absent or unreliable and assessment is difficult, baseline cortisol and DST determinations appear valid and may aid in diagnosis, if patients are *carefully* prescreened to eliminate false-positive nonsuppression. It may also be that some such individuals would benefit from adequate trials of antidepressant medication, with objective longitudinal clinical evaluation coupled with serial DSTs.

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An Analysis of DRG-Based Reimbursement for Psychiatric Admissions to General Hospitals

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The authors analyzed the potential financial impact of paying general hospitals on the basis of diagnosis-related groups (DRGs) for Medicare alcohol-drug abuse and psychiatric admissions. Average costs per admission were substantially higher for general hospitals with special psychiatric units that are currently exempt from the prospective payment system (PPS) than for hospitals without exempt units. Simulations of DRG-related payments indicated that these payments would be greater for admissions to hospitals with exempt psychiatric units than for admissions to hospitals without exempt units. However, the differences in costs between these two types of facilities were greater than the differences in payments that would occur under a PPS.

(Am J Psychiatry 1987; 144:603–609)

On Oct. 1, 1983, a prospective payment system (PPS) was introduced to pay for hospital stays of Medicare beneficiaries. Under this system, the level of payment is largely determined by the diagnosis-related group (DRG) into which the patient is classified. However, several adjustments are also made in calculating the amount of payment. As discussed in the paper by Mitchell et al. in this Special Section, nine of the 468 DRGs upon which payment is based are for psychiatric conditions, and five are for substance abuse.

Under the Medicare PPS, psychiatric hospitals are exempt from DRG-based payment, as are distinct-part psychiatric units of general hospitals that apply for an exemption and meet a number of requirements regarding staffing, record keeping, and courses of treatment. Alcohol and drug abuse hospitals and distinct-part units of general hospitals were also afforded the same exemptions, but only for a limited time. The five DRGs currently used for substance abuse became effective May 1, 1986, and represent a revision of the six previous DRGs. The simulations presented here do not incorporate this revision of the substance abuse DRGs.

Although psychiatric and substance abuse hospitals and units of general hospitals are currently exempt, consideration is being given to including them under DRG-based reimbursement. Taube et al. (1) documented differences in diagnosis, length of stay, and age between admissions to general hospitals with and to general hospitals without psychiatric units and differences between these types of facilities in a variety of characteristics such as size, ownership, and involvement in teaching. Consequently, it is important to analyze the differential financial impact of DRG-based reimbursement on these hospitals. In particular, it is useful to determine the impact on alcohol, drug abuse, and mental health (ADM) admissions of the various adjustments that are made to the basic DRG payment.

This analysis focuses on ADM admissions to general hospitals. According to data presented by Taube and Barrett (2), admissions to general hospitals account for approximately two-thirds of all psychiatric admissions under Medicare. In particular, the analysis focuses on the following questions: 1) What are the cost differences between admissions to general hospitals with

Presented at the 139th annual meeting of the American Psychiatric Association, Washington, D.C., May 10–16, 1986. Received April 30, 1986; revised Oct. 28, 1986; accepted Jan. 9, 1987. From Health Economics Research, Inc. Address reprint requests to Dr. Freiman, Health Economics Research, Inc., Suite 100, 75 Second Ave., Needham, MA 02194.

Supported by contract 278-84-0011(DB) from NIMH.
The authors thank Carl Taube for his comments.

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exempt units and those without exempt units? 2) How would the reimbursements for admissions to hospitals with exempt units differ from those for admissions currently covered by DRG-based payments if exempt units were included in the PPS?

METHOD

Data Collection

In order to perform accurate simulations of DRG-based payments for ADM admissions, it was necessary to combine a number of detailed data sources. The primary focus of our analysis was a data base containing the *universe* (not a sample) of 1982 Medicare Part A claims for Michigan, New Jersey, and North Carolina and 1983 Medicare claims for the state of Washington. These four states were chosen for study because they represented four different regions and because their size afforded us large populations. New Jersey was under a state-level PPS in 1982. However, there were a number of provisions that removed much of the prospective nature of payment, especially for ADM admissions. The following numbers of admissions were available for analysis: 6,939 in Michigan, 6,166 in North Carolina, 3,315 in Washington, and 6,790 in New Jersey.

The Medicare Part A claims include data on hospital identification, age and sex of the patient, primary and secondary diagnosis, primary surgical procedure, and hospital charges. The classification system developed by Fetter et al. (3) was used to place each patient into one of 468 DRGs. We then selected for analysis only those claims in major diagnostic categories 19 and 20 (DRGs 424–438)—that is, claims for patients with a principal diagnosis of an alcohol, drug abuse, or mental disorder.

DRG 424 (operating room procedures for patients who have a principal diagnosis of mental illness) contained a considerable number of cases in all four states. However, upon inspection, many of the specific procedures were found to be operations such as pacemaker insertions, cataract extractions, and hernia repairs that appear to be totally unrelated to a psychiatric disorder. Many of these admissions may end up in other, more appropriate (and often higher paying) DRGs as hospitals improve their diagnostic coding as a result of the PPS. Therefore, the analyses presented here exclude DRG 424.

Before the PPS, Medicare inpatient reimbursement was based not on actual charges but on the allowable cost of providing care. Since the claims data base contains only charge data, it was necessary to adjust these data by weighting charges according to the ratio of cost reimbursements to charges. Medicare Cost Reports provide the needed information on the ratio of costs to charges, as well as data on ownership, location, number of beds, teaching activities, type of facility, and utilization. The most recent year for which these data were available—fiscal year 1981—was used in the construction of cost-to-charge ratios and per diem costs. All of the dollar values were converted to 1982 dollars. The American Hospital Association's 1982 Annual Survey of Hospitals provided additional data for a number of variables, including the number of beds in special psychiatric or alcohol treatment units.

A list of hospitals that requested and received exemptions under the PPS for their psychiatric and/or alcohol and drug units, as of March 4, 1985, was obtained from the Health Care Financing Administration. The number of exempt psychiatric units in general hospitals was 37 for Michigan, 18 for North Carolina, 15 for Washington, and 14 for New Jersey. The number of exempt substance abuse units was 10 for Michigan, two for North Carolina, nine for Washington, and two for New Jersey. For ease of presentation, this paper uses the phrase "exempt hospital" to mean a hospital with an exempt unit.

The figures on exempt units for New Jersey are misleading because, as we have mentioned, New Jersey was already under its own PPS and thus received a waiver from the national PPS. Many hospitals that might qualify for exemptions have therefore not applied to the Health Care Financing Administration. Consequently, in the analyses for New Jersey the distinction is made between hospitals with and hospitals without special ADM units, according to American Hospital Association data, rather than between those with and those without exemptions. Analyses reported by us (M. Freiman, J. Mitchell, M. Rosenbach, et al.: "An Analysis of Patient Classification Systems for Prospective Rate-Setting and Simulations of Payment Outcomes for Psychiatric Admissions to General Hospitals," report submitted to Macro Systems under NIMH contract 278-84-001(DB), Oct. 30, 1985) indicate a fairly close correspondence between exemptions from the PPS and indications of a special unit in the 1982 American Hospital Association survey of hospitals for the other three states.

Simulation Method

The primary component of the PPS is the payment of a fixed amount for each hospital admission on the basis of one of the 468 DRGs. A number of adjustments are made to this base amount, depending on the urban or rural location of the hospital, the area wage level, costs of indirect medical education, and outlier admissions. It is these components and the basic standardized amount that were simulated in detail in this study.

Base DRG payment. A figure called the adjusted standardized amount is the basic amount of payment under the PPS. This is the amount that would be paid for a DRG that has a weight of 1.00. For each hospital, the adjusted standardized amount takes into account urban/rural location and local area wage levels. The base DRG payment for an admission is the product of

TABLE 1. DRG Mix for Exempt and Nonexempt Hospitals in Four States in 1982 or 1983[a]

Diagnosis-Related Group	Cases in Michigan (%)		Cases in North Carolina (%)		Cases in Washington (%)		Cases in New Jersey (%)	
	Exempt Hospitals[b]	Nonexempt Hospitals	Exempt Hospitals[b]	Nonexempt Hospitals	Exempt Hospitals[b]	Nonexempt Hospitals	Hospitals With Units[c]	Hospitals Without Units
425 Acute adjustment reactions	4.8	6.5	8.7	12.3	3.2	10.5	3.2	7.9
426 Depressive neuroses	16.7	10.6	18.7	15.4	6.0	12.2	13.4	13.3
429 Organic disturbances and mental retardation	19.4	28.6	22.6	32.6	11.2	25.4	8.7	24.2
430 Psychoses	37.3	22.8	25.8	10.4	51.2	32.4	53.0	22.5
438 Alcohol- and substance-induced organic mental syndrome	12.2	20.3	16.6	20.8	12.6	12.0	12.6	17.9

[a]Source: Medicare Part A claims, 1982, 1983.
[b]General hospital with a PPS-exempt psychiatric and/or alcohol-drug abuse unit.
[c]General hospital with a special psychiatric and/or alcohol-drug abuse unit, according to 1982 American Hospital Association data.

the weight for a specific DRG and the adjusted standardized amount.

Outlier payments. The PPS has provisions for two types of outlier payments: one for length of stay and the other for cost. If an admission qualifies as a length-of-stay outlier, it cannot be considered for payment as a cost outlier. Outlier payments provide only a portion of the costs incurred beyond the outlier threshold, which is defined for each DRG in terms of length of stay or cost. These payments are calibrated to comprise between 5% and 6% of total DRG-related payments under the PPS. The vast majority of this amount goes to length-of-stay outliers, with less than 1% of cases expected to qualify as cost outliers.

Indirect medical education. This component contains payments for costs related to teaching activities that are incurred by hospitals above and beyond the direct payments made to physicians. The indirect medical education component results from a calculation involving the number of residents per 100 beds and the combined value of the base and outlier payments.

Other adjustments. Our admissions and cost data were from 1982, while the dollar amounts in the *Federal Register* were for fiscal year 1985. These amounts were therefore deflated to 1982 levels by using a factor of 0.8075, derived from the inflation factors contained in various issues of the *Federal Register.*

The simulations were produced for a fully phased-in PPS. This means that payments were based 100% on a national rate. (During the phase-in period, there are payments based on hospital-specific costs and on regional payment rates.) The PPS currently pays for direct medical education costs and capital expenses on a pass-through basis. As a result, these costs were excluded from both our historical cost data and our PPS simulation calculations. In addition, the costs of kidney acquisition were ignored. (For a more detailed technical description of PPS reimbursement, see the *Federal Register,* Sept. 1, 1983, or Cromwell's discussion [4]. For the most recent PPS changes, see the *Federal Register,* Sept. 3, 1986.)

RESULTS

Descriptive Data

In all four states, hospitals with exempt units tended to have similar proportions of nonprofit, government, and for-profit ownership, as did hospitals without exempt units. However, hospitals with exempt units were substantially larger and were located in far more urbanized areas than hospitals without exempt units. Hospitals with exempt units were also much more heavily involved in teaching activities and as might be expected, had on average a larger number of Medicare ADM admissions.

Although the simulations were performed on admissions in all 15 ADM DRGs, five of the DRGs accounted for almost all admissions, and only two accounted for more than half of the total admissions. Consequently, we will focus on the five DRGs. In comparisons of hospitals with and hospitals without exempt units, the largest difference in DRG composition was between DRGs 429 and 430, as shown in table 1. DRG 430 (psychoses) accounted for 15%–19% more of the caseload for hospitals with exempt units than for hospitals without exempt units. For example, in North Carolina 25.8% of the cases in exempt hospitals were classified as psychoses, but only 10.4% in nonexempt hospitals were. Conversely, 9%–14% more of the caseload was accounted for by DRG 429 (organic disturbances and mental retardation) in nonexempt hospitals than in exempt hospitals. DRG 425 (acute adjustment reactions) represented a greater percentage of the caseload in nonexempt hospitals, although this difference was large only in Washington.

Table 2 indicates that for all ADM DRGs combined and for each individual DRG shown for Michigan, North Carolina, and Washington, the average cost per admission was much greater for hospitals with exempt units than for those without exempt units. For example, the average cost of an admission in North Carolina for DRG 430 was $1,717 in a nonexempt unit but $2,988 in an exempt unit. The differences were similar,

TABLE 2. Average DRG Costs for Exempt and Nonexempt Hospitals in Four States in 1982 or 1983[a]

Diagnosis-Related Group	Cost in Michigan ($)		Cost in North Carolina ($)		Cost in Washington ($)		Cost in New Jersey ($)	
	Exempt Hospitals[b]	Nonexempt Hospitals	Exempt Hospitals[b]	Nonexempt Hospitals	Exempt Hospitals[b]	Nonexempt Hospitals	Hospitals With Units[c]	Hospitals Without Units
425 Acute adjustment reactions	3,976	1,482	2,806	1,110	1,535	1,263	1,683	1,175
426 Depressive neuroses	3,971	2,591	3,196	1,317	1,979	1,323	2,063	1,851
429 Organic disturbances and mental retardation	3,376	2,526	2,504	1,706	2,791	1,578	3,301	3,054
430 Psychoses	4,614	3,616	2,988	1,717	2,992	1,824	2,814	1,884
438 Alcohol- and substance-induced organic mental syndrome	2,757	2,223	1,686	1,007	3,001	1,235	1,846	1,924
Total	3,952	2,663	2,632	1,418	2,899	1,546	2,576	2,232

[a]Source: Medicare Part A claims, 1982, 1983.
[b]General hospital with a PPS-exempt psychiatric and/or alcohol-drug abuse unit.
[c]General hospital with a special psychiatric and/or alcohol-drug abuse unit, according to 1982 American Hospital Association data.

TABLE 3. Average Length of Stay for DRGs for Exempt and Nonexempt Hospitals in Four States in 1982 or 1983[a]

Diagnosis-Related Group	Length of Stay in Michigan (days)		Length of Stay in North Carolina (days)		Length of Stay in Washington (days)		Length of Stay in New Jersey (days)	
	Exempt Hospitals[b]	Nonexempt Hospitals	Exempt Hospitals[b]	Nonexempt Hospitals	Exempt Hospitals[b]	Nonexempt Hospitals	Hospitals With Units[c]	Hospitals Without Units
425 Acute adjustment reactions	14.6	6.7	11.5	7.1	6.2	5.0	9.4	6.3
426 Depressive neuroses	18.1	12.7	15.2	8.8	9.5	6.1	12.7	11.5
429 Organic disturbances and mental retardation	13.4	11.4	13.0	11.5	12.4	7.0	17.9	17.5
430 Psychoses	20.4	17.2	16.0	12.0	13.8	8.5	16.9	11.8
438 Alcohol- and substance-induced organic mental syndrome	11.5	9.2	7.9	6.3	14.7	5.2	10.2	9.9
Total	17.0	12.2	13.1	9.2	13.8	7.0	15.0	12.6

[a]Source: Medicare Part A claims, 1982, 1983.
[b]General hospital with a PPS-exempt psychiatric and/or alcohol-drug abuse unit.
[c]General hospital with a special psychiatric and/or alcohol-drug abuse unit, according to 1982 American Hospital Association data.

but of smaller magnitude, in New Jersey for hospitals with and hospitals without special units. Comparisons such as these are at least in part a reflection of differences in length of stay, which were similar in direction and magnitude, as shown in table 3.

Admission-Level Simulation Analysis

Table 4 presents the average values of the simulated DRG-related payments for ADM admissions to general hospitals with and general hospitals without exempt units. The top part of the table compares the actual 1982 or 1983 Medicare cost with the simulated PPS payment.

For example, in North Carolina the average cost of admissions to hospitals with exempt units was $2,632. The average simulated DRG payment is $2,449, or $183 less than the average cost for this group. The average simulated DRG payment is substantially lower for nonexempt hospitals in North Carolina, $1,832 versus $2,449. However, because the actual average cost in 1982 was only $1,418 for this group, the DRG payment would exceed the actual 1982 value by $414.

In all states the average DRG payment would be substantially greater for exempt units than for nonexempt units. In Michigan, this still means that for both types of hospitals the average simulated DRG payment falls short of the actual cost. In both North Carolina and Washington, the difference is negative for admissions to exempt hospitals but positive for nonexempt hospitals. Finally, for New Jersey, the difference is positive for both types of hospitals. *In all states the gap between average costs for exempt and nonexempt hospitals is greater than the simulated DRG payment differential between these two groups.*

The actual payments presented in table 4 indicate not only differences between hospitals with and hospitals without exempt units but also differences across states. The simulated DRG payments track much of this difference, but clearly not in an exact fashion. For example, the average admission in 1982 cost $1,320 more in an exempt hospital in Michigan than in one in North Carolina ($3,952 minus $2,632), while the average simulated DRG payment in Michigan is only $699 higher than it is in North Carolina ($3,148 minus $2,449).

TABLE 4. Simulation of DRG-Related Payments[a] for Psychiatric Admissions to Exempt and Nonexempt Hospitals in Four States in 1982 or 1983[b]

Item	Michigan		North Carolina		Washington		New Jersey	
	Exempt Hospitals[c]	Nonexempt Hospitals	Exempt Hospitals[c]	Nonexempt Hospitals	Exempt Hospitals[c]	Nonexempt Hospitals	Hospitals With Unit[d]	Hospitals Without Unit
Average Medicare cost ($)	3,952	2,663	2,632	1,418	2,899	1,546	2,910	2,386
Average simulated DRG payment ($)	3,148	2,563	2,449	1,832	2,758	2,074	3,210	2,915
Difference (DRG payment minus actual payment) ($)	−804	−100	−183	+414	−141	+528	+300	+529
Base DRG payment ($)[e]	2,582	2,468	2,102	1,931	2,519	2,151	2,610	2,596
Adjustments to base payment								
Case-mix variation ($)	−86	−160	−128	−188	−28	−111	−14	−171
Indirect medical education ($)	380	145	346	56	149	21	278	129
Outliers ($)	272	110	129	33	118	13	336	361

[a]Figures are in 1982 dollars.
[b]Source: Medicare Part A claims, 1982, 1983.
[c]General hospital with a PPS-exempt psychiatric and/or alcohol-drug abuse unit.
[d]General hospital with a special psychiatric and/or alcohol-drug abuse unit, according to 1982 American Hospital Association data.
[e]Amount that would have been paid if each admission had DRG weight of 1.00.

The bottom part of table 4 presents the components of the total simulated DRG payment. The base DRG payment only takes into account the urban/rural location of the hospital to which patients are admitted and the adjustment for local area wage rates. Another way of looking at this rate is that it is the amount that would be paid if each admission had a DRG weight of 1.00. In North Carolina, there would be a $171 difference ($2,102 minus $1,931) in this base rate between exempt and nonexempt hospitals.

The case-mix variation row in table 4 indicates the amount of payment that would result from a DRG mix whose average weight is different from 1.00. In all columns this component is negative, indicating the relatively low weights assigned to ADM DRGs. In North Carolina, to take an example, this component lowers the average simulated payment by $128 for exempt hospitals and by $188 for nonexempt hospitals, indicating that exempt hospitals have a more complex average case mix.

The indirect medical education component is substantially greater on average for admissions to exempt hospitals than for admissions to nonexempt hospitals. In North Carolina, the average simulated indirect medical education payment per admission is $346 for exempt hospitals but only $56 for nonexempt hospitals.

Finally, the outlier component is the sum of both the cost and length-of-stay outlier payments, averaged over all admissions in the category. In North Carolina the outlier payments would amount to $129 per admission for exempt hospitals but only $33 for nonexempt hospitals. Summing all these components yields the simulated DRG payment shown in the top half of table 4.

A more detailed analysis of outlier payments revealed that the average payment for admissions that actually received outlier payments was roughly the same for admissions to exempt and admissions to nonexempt hospitals. The difference in the average outlier payment per admission shown in table 4, therefore, results primarily from the substantially greater probability of outlier payments occurring in hospitals with exempt units. The proportion of admissions to exempt hospitals receiving outlier payments ranged from 5% in Washington to 12% in Michigan.

Hospital-Level Analysis

The preceding section presented admissions-level results averaged over all admissions in a category. It is also of interest to perform a hospital-level analysis—that is, to analyze the simulation results by grouping together all of the admissions to a hospital and determining the average impact on that hospital. The hospital is the organization that provides inpatient services, so a hospital-level analysis is most relevant to issues of access to care. If certain types of facilities—whether defined by type of ownership, by geographic location, or by other characteristics—are financially stressed under DRG-based payment, persons served by those hospitals might find themselves without reasonably accessible inpatient psychiatric care.

The hospital-level analysis presented here gives each hospital equal weight, in contrast to the previous analysis, in which each admission was given equal weight. The results of these two analyses will differ to the degree that all hospitals do not have the same number of psychiatric admissions. However, so that this analysis would not give undue emphasis to hospitals that have almost no involvement with Medicare ADM patients, hospitals with fewer than 15 Medicare ADM admissions were excluded.

For each hospital the average actual cost per admission was compared to the average simulated PPS payment per admission. The term "winner" is used to describe a hospital for which the simulated PPS payment exceeds actual costs, and the term "loser" is used

TABLE 5. Simulation of Average Gains and Losses From DRGs by Type of Hospital[a] in Four States in 1982 or 1983[b]

Type of Hospital	Michigan	North Carolina	Washington	New Jersey[c]
All hospitals				
Number of hospitals	94	103	38	65
Average cost ($)	2,945	1,602	1,968	2,595
Average gain (loss) ($)	(255)	333	384	444
Winners (%)[d]	48	79	82	77
Losers (%)[d]	52	21	18	23
Hospitals with exempt units				
Number of hospitals	34	18	13	42
Average cost ($)	3,923	2,650	2,853	2,891
Average gain (loss) ($)	(757)	(64)	(68)	241
Winners (%)[d]	26	50	46	69
Losers (%)[d]	74	50	54	31
Hospitals without exempt units				
Number of hospitals	60	85	25	23
Average cost ($)	2,391	1,380	1,508	2,056
Average gain (loss) ($)	29	417	619	315
Winners (%)[d]	60	85	100	91
Losers (%)[d]	40	15	0	9

[a]Excludes hospitals with less than 15 Medicare alcohol, drug abuse, and psychiatric admissions and cases in DRG 424.
[b]Source: Medicare Part A claims, 1982, 1983.
[c]Because New Jersey has a waiver from PPS, comparisons are between hospitals with and without special units, according to 1982 American Hospital Association data.
[d]Winning (or losing) hospitals are defined as having a simulated DRG payment that is greater than (or less than) actual costs.

when the simulated payment is less than actual costs. It should be noted that the term "loser" does not mean that the hospital actually has to pay out some amount, but rather that its revenues would be less under the simulated DRG payment system than it would have been under the cost-based reimbursement system that existed in 1982.

The hospital-level calculations are presented in table 5. For all hospitals in North Carolina, for example, the average cost per ADM admission is $1,602, and the average gain would be $333. Seventy-nine percent of the hospitals would be winners and only 21% would be losers.

Turning to the rows for the hospitals without exempt units, we find that the average change in payment per admission in all four states would be clearly positive. Furthermore, the vast majority of losing hospitals in this category would be located in Michigan.

However, a different picture emerges for hospitals with exempt ADM units. In Michigan there would be a substantial average loss of $757, while in both North Carolina and Washington there would be small average losses. Only for New Jersey hospitals with special units would there be an average gain per admission. In Michigan approximately 75% of exempt hospitals would be losers, while in North Carolina and Washington approximately half would be losers.

The characteristics of hospitals that were winners or losers by a substantial amount were analyzed in greater detail. In particular, we focused on those hospitals for which the average DRG payment would differ from actual costs by more than 20%. As might be expected from the analyses presented here, the majority of substantial losers were hospitals with exempt units. However, there were also some nonexempt hospitals in this category. By the same token, not all substantial winners would be hospitals without exempt units. Compared to hospitals that were substantial winners, substantial losers were also more likely to be larger, to treat more severely ill patients (as indicated by a higher case-mix index), to be located in urban areas, to have a greater involvement in teaching activities, and to have a larger caseload of Medicare psychiatric patients.

DISCUSSION

DRG-based payments for admissions to general hospitals with exempt units would on average fall short of the historical costs of treating these patients. The adjustments to the basic payment amount for urban/rural location, area wage rates, indirect medical education costs, and outlier cases all increase payments for admissions to hospitals with exempt units relative to payments for admissions to hospitals without such units, but these adjustments cover, on average, only a portion of the differences in cost between these two types of facilities.

Comparisons of costs with simulated DRG-based payments can be viewed as indicating the degree of financial stress that would be placed on hospitals under a PPS. However, such comparisons do not indicate the ultimate degree of financial benefit or hardship, because hospitals are expected to respond to the changed incentives of prospective payment. Indeed, the magnitude of the average loss for most of the exempt hospitals is no more than the cost of 1 or 2 days of hospitalization. Hospitals may therefore be well able to reduce costs until they equal payments. Additional research is required to determine whether

such reductions would represent increased efficiency or undertreatment.

The simulations provide clear justification for the concerns that led to the exemption of special ADM units in general hospitals from PPS payment. These exempt ADM units appear to treat patients who are, on average, more severely ill than those treated in nonexempt locations. If exempt hospitals experience financial hardship under a PPS in treating psychiatric patients, they will be more likely to provide less definitive treatment and possibly engage in more selective admissions policies in an attempt to screen out patients who are expected to have high treatment costs. At the extreme, exempt psychiatric units in some general hospitals might even close down. These responses on the part of providers might create problems of access for the psychiatric patients who are most in need of care.

At the same time that costs for exempt facilities exceed simulated payments on average, a number of other factors are at work; not all exempt hospitals would lose under a PPS, and not all nonexempt hospitals would gain. Of particular note are the different state-level effects of using a basic payment for each DRG that is uniform (before area cost adjustments) across the nation. Of the four states we analyzed, Michigan had the hospitals with the highest average cost per admission—both exempt and nonexempt hospitals. As a result, the PPS simulation produced results for Michigan that are the least favorable among the four states.

One of the premises of a PPS is that not all geographic variation is the result of justifiable differences in treatment patterns or input costs. It would therefore not be appropriate to use the tracking of regional cost patterns as a rigid evaluation criterion. Further research is required to determine the degree to which higher costs are the result of differences in characteristics of patients, input costs, and appropriate variations in treatment patterns.

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Bringing Psychiatric Patients Into the Medicare Prospective Payment System: Alternatives to DRGs

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The basis of Medicare's prospective payment for alcohol, drug abuse, and mental illness hospital admissions has been the patient classification system known as diagnosis-related groups (DRGs). This paper describes two alternative patient classification systems, disease staging and clinically related groups, and reports how well each system predicts resource use compared to the DRG system. Medicare data from four states were used to test the comparative strength of these patient classification systems. Although disease staging and clinically related groups performed better than DRGs, they were still poor predictors of resource use.

(Am J Psychiatry 1987; 144:610–615)

Prospective payment for hospital services to Medicare patients was mandated by Public Law 98-21. The implementation of this law began for most hospitals on Oct. 1, 1983; it uses a pricing system linked to diagnosis at discharge (1). For the purpose of determining the amount of reimbursement, a classification system developed by Fetter et al. is used to categorize diagnoses into 468 diagnosis-related groups (DRGs) (2). At the time of implementation, concerns were raised about the use of DRGs as a basis of prospective payment for medical and surgical care (3–5). Additional concerns were raised about the appropriateness of the prospective payment system (PPS) for psychiatric patients in special units and free-standing facilities, since there was no previous experience upon which to draw (statement by APA before the Subcommittee on Health, Ways and Means Committee, House of Representatives, Feb. 15, 1983).

As a result of these concerns, Congress granted an exemption from the PPS for psychiatric hospitals and also permitted psychiatric and substance abuse units in general hospitals to apply for an exemption. The Department of Health and Human Services was asked to report to Congress by the end of 1985 on the feasibility of including these facilities and specialty units in the Medicare PPS (6). In response to that request, the National Institute of Mental Health (NIMH) and the Health Care Financing Administration funded a number of studies, including the one reported here. Some of the work from this study is reported by Freiman et al. and McGuire et al. elsewhere in this Special Section.

This paper describes and evaluates alternative patient classification systems that could be used either to refine or to replace the current psychiatric and substance abuse DRGs. According to the developers of DRGs (2), this classification system is expected to have the following attributes: 1) it should be medically meaningful, 2) classes of patients should be grouped together on the basis of variables that are commonly available in hospital discharge abstracts, 3) there should be a manageable number of diagnostic groups, 4) each group should be comparable across the different coding schemes, and 5) class definitions should be comparable across the different coding schemes. Alternative systems were reviewed and tested in this study because of questions about how well DRGs fulfill these criteria in psychiatric and substance abuse admissions.

Although there are many such systems available for research, this analysis was limited to those that were computerized and that used the Uniform Hospital Discharge Data Set and thus could be quickly integrated into a PPS. This rules out the Severity of Illness Index (7), which requires the use of clinical judgment and the abstraction of data from patients' records. Only two existing classification approaches other than DRGs met the requirements: disease staging, developed by Systemetrics (8), and patient management categories, developed at Blue Cross of Western Pennsylvania (9). However, at the time the study began, the patient management categories software was not available to us, so this paper reports a comparison of existing DRGs with the Systemetrics disease staging system and with a revised patient classification system that we developed, which is called clinically related groups (CRGs).

Received April 30, 1986; revised Sept. 15, 1986; accepted Oct. 17, 1986. From Health Economics Research, Inc.; and the Department of Psychiatry, Harvard Medical School, Boston, Mass. Address reprint requests to Dr. Mitchell, Health Research Economics, Inc., Suite 100, 75 Second Ave., Needham, MA 02194.

Supported by contract 278-84-0011(DB) from NIMH.

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TABLE 1. Distribution of General Hospital Discharges Across DRGs in Four States in 1982[a]

Diagnosis-Related Group	Discharges (%)
425 Acute adjustment reactions and disturbances of psychosocial dysfunction	6.7
426 Depressive neuroses	13.5
427 Neuroses except depressive	0.8
428 Disorders of personality and impulse control	1.4
429 Organic disturbances and mental retardation	22.5
430 Psychoses	33.7
431 Childhood mental disorders	0.3
432 Other diagnoses of mental disorders	0.6
433 Substance use and substance-induced organic mental disorders; left against physician's advice	0.1
434 Drug dependence	0.4
435 Drug use except dependence	0.2
436 Alcohol dependence	2.7
437 Alcohol use except dependence	1.1
438 Alcohol- and substance-induced organic mental syndrome	16.0

[a]Source: Medicare Part A claims, 1982, for Michigan, New Jersey, North Carolina, and Washington.

METHOD

We compared the three different classification systems for more than 22,000 Medicare general hospital admissions for psychiatric problems and substance abuse in 1982 in Michigan, New Jersey, North Carolina, and Washington. These states were chosen to represent each of the major regions of the country. Claims coded as operating room procedures for patients who had mental illness as their primary diagnosis (DRG 424) were excluded from this analysis. Hospital costs reported here have been adjusted to reflect Medicare reasonable costs, according to each hospital's Medicare Cost Report. The development of clinically related groups reported here was based on Michigan admissions alone (N=6,939).

RESULTS

Diagnosis-Related Groups

DRGs were developed as a case-mix measure in acute-care hospitals (2). As a patient classification scheme, the purpose of this system is to identify a set of case types, each representing a class of patients with expected similarities in utilization of resources and length of stay. Fetter and his colleagues constructed the DRGs through an iterative process that used, in turn, computerized information processing, physician judgment, and statistical algorithms. Table 1 shows each substance abuse and psychiatric DRG by number and title and the relative distribution of discharges across the four study states.

Two DRGs, organic disturbances and mental retardation (DRG 429) and psychoses (DRG 430) accounted for more than half of all discharges (56%). Acute adjustment reactions (DRG 425) and depressive neuroses (DRG 426) accounted for 20% of the discharges. The largest substance abuse category was DRG 438, alcohol- and substance-induced organic mental syndrome. Virtually all of the remaining DRGs had very few discharges. In separate analyses not reported here, it was found that some DRG categories contained a substantial number of cases with nonspecific diagnoses. For example, more than 27% of Medicare patients whose discharge diagnosis was psychosis (DRG 430) were coded as *ICD-9* 298.9, or unspecified psychosis.

Tables 2 and 3 present average hospital costs and length of stay, respectively, for the six most frequent substance abuse and psychiatric DRGs. Psychoses (DRG 430) generally had the highest costs and longest stays. The coefficients of variation for hospital costs were generally quite high, however—about 1.0. The coefficient of variation provides a standardized measure for comparing variation across groups with different means and is defined as the standard deviation divided by its mean. High coefficients of variation indicate more cost variability within a DRG and hence imply greater heterogeneity in resource use.

Systemetrics's Disease Staging

Disease staging seeks to distinguish clinically significant levels of severity that might predict resource use more accurately than DRGs do. All diseases are organized into four generic levels of severity: stage 1, conditions with no complications or with problems of minimal severity; stage 2, problems limited to an organ or system, with a considerably higher risk of complications than in stage 1; stage 3, multiple site involvement, with generalized systemic involvement and poor prognosis; stage 4, death. The staging algorithm reviews all listed diagnoses, decides which is the principal diagnosis, and then assigns that diagnosis to a disease category. There are approximately 1,000 categories, based on disease etiology. Each category is then staged on a scale of 1 to 4, depending on the specific principal *ICD-9* code and the presence of particular related secondary diagnoses. The major advantage of this classification approach is that it considers the interrelationship of multiple diagnoses.

Table 4 shows how disease staging treats discharges in DRGs 429 (excluding mental retardation) and 430. For ease of presentation, we have excluded the stages for which there were no cases in our sample. For some categories, stages are based on principal diagnosis alone; a diagnosis of simple schizophrenia (in disease category 247) is stage 1, whereas a diagnosis of residual schizophrenia is stage 2. Other categories require multiple diagnoses for staging. For example, stage 2 of chronic brain syndrome (disease category 224) requires a primary diagnosis of organic brain syndrome plus a secondary diagnosis of psychoses not otherwise specified. As shown in table 4, the cases in DRG 429 (organic disturbances) are distributed across a number of disease categories that are quite similar to

TABLE 2. Mean General Hospital DRG Costs in Four States in 1982[a]

Diagnosis-Related Group	Michigan		New Jersey		North Carolina		Washington	
	Mean Cost ($)	CV[b]	Mean Cost ($)	CV[b]	Mean Cost ($)	CV[b]	Mean Cost ($)	CV[b]
425 Acute adjustment reactions and disturbances of psychosocial dysfunction	2,612	1.18	1,769	0.92	1,577	1.46	1,350	0.91
426 Depressive neuroses	3,878	1.13	2,522	0.84	2,060	1.21	1,614	0.96
429 Organic disturbances and mental retardation	3,012	1.00	3,287	1.30	1,922	0.97	2,085	0.92
430 Psychoses	4,372	1.00	3,061	1.02	2,443	1.07	2,664	1.01
436 Alcohol dependence	3,453	1.07	2,651	0.76	1,357	1.11	3,493	0.44
438 Alcohol- and substance-induced organic mental syndrome	2,512	1.18	2,087	1.09	1,210	1.47	2,347	0.86

[a]Source: Medicare Part A claims, 1982.
[b]CV=coefficient of variation.

TABLE 3. Mean Length of Stay in General Hospitals for DRGs in Four States in 1982[a]

Diagnosis-Related Group	Michigan		New Jersey		North Carolina		Washington	
	Length of Stay (days)	CV[b]	Length of Stay (days)	CV[b]	Length of Stay (days)	CV[b]	Length of Stay (days)	CV[b]
425 Acute adjustment reactions and disturbances of psychosocial dysfunction	10.1	1.01	9.7	0.92	8.3	0.91	5.4	0.92
426 Depressive neuroses	16.0	0.77	15.3	0.85	11.3	0.88	7.6	1.00
429 Organic disturbances and mental retardation	12.2	0.84	18.2	1.36	11.9	0.83	9.2	0.91
430 Psychoses	19.2	0.80	18.5	0.99	14.3	0.78	12.3	0.96
436 Alcohol dependence	13.2	0.76	15.3	0.78	7.7	0.83	18.4	0.44
438 Alcohol- and substance-induced organic mental syndrome	10.0	0.89	10.8	0.98	6.8	0.84	11.2	0.92

[a]Source: Medicare Part A claims, 1982.
[b]CV=coefficient of variation.

one another (chronic brain syndrome, Alzheimer's disease, senility, dementia, and delirium) but tend to cluster in the first, largely because the uncomplicated senile dementia cases are assigned by the computer algorithm to stage 3 of chronic brain syndrome. DRG 430 cases, on the other hand, are distributed fairly evenly across four categories: depression, manic-depressive psychosis, schizophrenia, and paranoid schizophrenia.

Table 5 presents mean hospital costs and length of stay by stage for the five most frequent disease categories. Except for deaths, which are always more expensive, there is no consistent evidence that increasing costs are associated with higher level stages. However, stage 3 depressions and stage 3 manic-depressive psychoses are more expensive than stage 1 cases in the same disease categories.

Clinically Related Groups

On the basis of clinical judgment and experience, two of us (B.L. and L.I.S.) attempted to develop a revised version of DRGs based on groupings that were more clinically homogeneous. The attempt to disaggregate and reformulate diagnostic groups focused on those with high volume under Medicare. Table 6 shows the resulting CRGs. Some CRGs are identical to DRGs; for example, we found that DRG 426 (depressive neuroses) could not be divided according to patients' age or presence of a secondary medical diagnosis into subgroups with significantly different hospital costs. Similarly, meaningful subgroups could not be constructed within DRG 429 (organic disturbances). There were no significant differences in utilization of resources on the basis of age, secondary medical problems, or psychotic versus nonpsychotic diagnoses.

Major revisions were made within DRG 430 (psychoses), which had the largest number of discharges. We began by subdividing this group into four diagnostic categories, two of which were further subdivided into the age categories of under 65 years and 65 years and older. Since Medicare patients include both the elderly and the disabled (including those disabled by virtue of mental illness), this age split was used as a proxy for chronicity. The alcoholism DRGs (numbers 436–438) were also redefined by combining all discharge diagnoses of alcohol dependence and abuse and then dividing them into two groups according to patients' age: under 65 and 65 years and older (CRGs 14 and 15). CRG 16 was given the same title as DRG 438 (alcohol- and drug-induced organic brain syndrome) but consists solely of patients with an acutely altered mental status due to substance use. Discharges with alcohol- and drug-induced dementia were moved to organic disturbances (CRG 4).

Hospital costs and length of stay for all CRGs are

TABLE 4. Distribution of DRGs 429 and 430 According to Disease Staging (8) in Michigan in 1982[a]

Disease Category/Stage	Diagnosis-Related Group: 429 Organic Disturbances (%)	Diagnosis-Related Group: 430 Psychoses (%)
224 Chronic brain syndrome		
Stage 1. Unspecified organic brain syndrome	51.8	0.0
Stage 2. Stage 1 plus psychoses not otherwise specified	1.3	0.3
Stage 3. Stage 1 plus senile dementia	28.6	0.0
Stage 4. Death	1.7	0.0
225 Alzheimer's disease		
Stage 3. Senile dementia	10.1	0.0
Stage 4. Death	0.4	0.0
236 Senility		
Stage 3. Stage 2 plus malnutrition, coma	0.2	0.0
239 Dementia		
Stage 1. Senile dementia not otherwise specified	0.2	0.0
Stage 3. Alcohol amnesia, Korsakoff's disease, or stage 2 plus physical symptoms	1.3	0.0
240 Delirium		
Stage 1. Presenile dementia	0.2	0.0
Stage 3. Stage 1 plus cerebral degeneration	1.3	0.0
Stage 4. Death	0.1	0.0
241 Depression		
Stage 1. Neurotic depression	0.5	1.3
Stage 3. Major depressive disorder (psychosis)	0.4	13.4
245 Manic-depressive psychosis		
Stage 1. Manic, excitative disorder	0.0	17.6
Stage 3. Recurrent depressive disorder	0.2	21.0
Stage 4. Death	0.0	0.7
247 Schizophrenia		
Stage 1. Simple, acute	0.0	13.3
Stage 2. Residual, chronic	0.0	7.4
Stage 3. Chronic	0.0	8.9
248 Paranoid schizophrenia		
Stage 1. Paranoid type, delusions	0.6	16.1

[a]Source: Medicare Part A claims, Michigan, 1982.

shown in table 7. The average hospital costs for the five new adult psychosis categories (CRGs 5–9) were quite different from one another, ranging from $3,697 to $5,721; the DRG mean was $4,372. When the over/under age 65 split was used to subcategorize a diagnostic grouping, the data indicated that older patients stayed in the hospital longer and cost more to treat than did younger disabled patients with similar diagnoses. Nevertheless, the coefficients of variation around each CRG remain as large as those for DRGs.

Comparative Explanatory Power

The critical question for Medicare payment purposes is whether the CRG or the disease staging model performs any better than the DRGs used by Medicare. Table 8 summarizes the comparative ability of these three classification approaches to explain the variation in hospital costs and in length of stay. Both disease staging and CRGs appear to be superior to DRGs in the percentage of variation explained (as measured by the R^2), but most (approximately 90%) of the variation is still unexplained. These small improvements are not very meaningful for reimbursement purposes.

DISCUSSION

Concerns have been raised about the appropriateness of the DRG classification system for psychiatric care. Studies, including the one reported here, have consistently shown that DRGs explain less than 10% of the variation in hospital costs or in length of stay for psychiatric patients (10–14). As a result, NIMH and the Health Care Financing Administration were interested in testing the potential usefulness of other patient case-mix systems. Two alternative classification systems (disease staging and CRGs) were only marginally superior to DRGs in their ability to predict hospital costs, however.

The characteristic which all three of these classification systems share is that they are based on *ICD-9* coded diagnoses; there are a number of reasons why these diagnoses may not be strongly related to costs. First, the *ICD-9* nomenclature provides no clinical guidelines or behavioral criteria for the diagnosis of mental disorders. Furthermore, the inclusion of disorders, symptoms, and pathological processes in the terminology causes considerable overlap in possible coding choices. This may be desirable for a coding system intended to capture the nature of the medical problem that created the need for hospitalization, but it has obvious limitations when used for grouping together diagnoses that are supposed to represent distinct levels of resource use.

Second, a diagnosis alone does not capture important variables such as the severity of symptoms and the availability of nonhospital supports for the patient. There is limited consensus on the ability to generalize appropriate treatment settings for patients who have the same diagnosis and severity of illness. Clinical decisions are affected by the training and experience of the physician, the availability of alternatives to hospitalization, local customary practice, and other factors.

Finally, differences in treatment goals affect utilization of resources in different settings; for example, Goldman et al. (15) have pointed out that alcoholic patients with the same diagnosis can be admitted for a brief detoxification or for a longer alcohol rehabilitation program. For this reason, the Health Care Financing Administration has already incorporated this distinction in its plans to phase alcohol treatment programs into DRG-based reimbursement. The rationale is clearly that rehabilitation may lead to more lasting improvements and obviate the need for repeated hospitalizations for detoxification. This same reasoning might be used to justify longer stays in other specialized psychiatric programs.

TABLE 5. Mean Hospital Costs and Length of Stay for Selected Disease Categories/Stages in Michigan in 1982[a]

Disease Category/Stage	Hospital Cost		Length of Stay	
	Mean ($)	CV[b]	Mean (days)	CV[b]
224 Chronic brain syndrome				
Stage 1. Unspecified organic brain syndrome	2,986	0.94	12.3	0.86
Stage 2. Stage 1 plus psychoses not otherwise specified	3,426	1.05	13.5	0.80
Stage 3. Stage 1 plus senile dementia	2,935	1.17	11.5	0.86
Stage 4. Death	4,527	1.06	10.0	0.89
241 Depression				
Stage 1. Neurotic depression	3,829	1.14	15.8	0.80
Stage 2. Stage 1 plus personality disorder or substance abuse	3,087	0.67	13.9	0.50
Stage 3. Major depressive disorder (psychosis)	4,929	0.95	21.8	0.68
Stage 4. Death	7,961	0.65	19.3	0.52
245 Manic-depressive psychosis				
Stage 1. Manic, excitative disorder	3,395	0.97	12.6	0.85
Stage 3. Recurrent depressive disorder	5,480	0.98	23.4	0.71
Stage 4. Death	10,568	1.58	19.3	1.05
247 Schizophrenia				
Stage 1. Simple, acute	4,227	0.86	19.9	0.79
Stage 2. Residual, chronic	3,987	0.89	19.3	0.84
Stage 3. Chronic	3,954	0.94	20.1	0.93
248 Paranoid schizophrenia				
Stage 1. Paranoid type, delusions	3,965	0.96	18.2	0.79

[a]Source: Medicare Part A claims, Michigan, 1982.
[b]CV=coefficient of variation.

TABLE 6. Classification of Admissions According to Clinically Related Groups (CRGs) in Michigan 1982[a]

CRG	Description	Percent of All Admissions
1 Depressive neuroses	Unchanged from DRG 426	13.9
2 Anxiety and other neuroses	Includes all of DRG 425 (except acute delirium, transient organic mental syndrome, and hallucinations) plus all of DRG 427	6.2
3 Personality disorders	Includes all of DRG 428 plus eating disorders (formerly in DRG 432)	1.4
4 Organic disturbances	Includes all of DRG 429 (except mental retardation) plus acute delirium and transient organic mental syndrome (formerly in DRG 425) plus alcohol amnesia and Korsakoff's disease (formerly in DRG 438)	25.0
5 Paranoid psychoses	Includes paranoid psychoses (about 20% of cases in DRG 430) plus hallucinations (formerly in DRG 425)	6.9
6 Schizophrenia, excluding schizoaffective, age 65 and older	Includes all schizophrenia diagnoses, except schizoaffective type, in persons age 65 years and older (about 5% of cases in DRG 430)	1.7
7 Schizophrenia, excluding schizoaffective, age under 65	As in CRG 6, except only in persons under 65 years of age (about 33% of cases in DRG 430)	10.4
8 Bipolar, affective psychoses, schizoaffective disorders, age 65 and older	Includes all bipolar and affective disorders, plus schizoaffective-type schizophrenia, in persons age 65 years and older (about 25% of cases in DRG 430)	7.2
9 Bipolar, affective psychoses, schizoaffective disorders, age under 65	As in CRG 8, except in persons under 65 years of age (about 15% of cases in DRG 430)	5.3
10 Childhood psychoses	Includes all diagnoses of childhood psychoses (from DRG 430); no cases in our sample	0.0
11 Conduct and developmental disorders	Includes mental retardation (formerly in DRG 429) and conduct disorders (formerly in DRG 431)	0.6
12 Sleep and sexual disorders	Includes sleep and sexual disorders (formerly in DRG 431)	0.3
13 Drug use/dependence	Includes all of DRGs 434 and 435 (except drug-induced organic brain syndrome)	0.7
14 Alcohol use/dependence, age 65 and older	Includes all cases of alcohol dependence and abuse in persons age 65 years and older (about 55% of cases in DRGs 436 and 437 and 25% of DRG 438)	6.8
15 Alcohol use/dependence, age under 65	As in CRG 14, except in persons under 65 years of age (about 45% of cases in DRGs 436 and 437 and 20% of DRG 438)	5.3
16 Alcohol- and drug-induced organic brain syndrome	Includes all cases of acute intoxication	8.2

[a]Source: Medicare Part A claims, Michigan, 1982.

While the poor predictive power of DRGs is discouraging, this does not necessarily mean that general hospitals which treat psychiatric patients would fare poorly under prospective payment. Actual payments under the Medicare PPS are based on many other factors besides the patient's DRG category, including

TABLE 7. Mean Hospital Costs and Length of Stay for Clinically Related Groups (CRGs) in Michigan in 1982[a]

CRG	Hospital Costs		Length of Stay	
	Mean ($)	CV[b]	Mean (days)	CV[b]
1 Depressive neuroses	3,878	1.13	16.0	0.78
2 Anxiety and other neuroses	2,690	1.21	10.5	1.00
3 Personality disorders	3,276	1.03	13.8	0.93
4 Organic disturbances	3,035	1.03	12.2	0.84
5 Paranoid psychoses	3,697	1.18	13.6	0.89
6 Schizophrenia, excluding schizoaffective, age 65 and older	4,386	0.77	21.4	0.71
7 Schizophrenia, excluding schizoaffective, age under 65	3,866	0.93	18.7	0.87
8 Bipolar, affective psychoses, schizoaffective disorders, age 65 and older	5,721	0.99	24.7	0.69
9 Bipolar, affective psychoses, schizoaffective disorders, age under 65	4,521	0.83	20.0	0.66
10 Childhood Psychoses	—		—	
11 Conduct and developmental disorders	2,475	0.92	10.8	0.96
12 Sleep and sexual disorders	2,214	1.09	5.3	1.09
13 Drug use/dependence	3,187	0.78	12.8	0.71
14 Alcohol use/dependence, age 65 and older	3,095	0.93	12.8	0.78
15 Alcohol use/dependence, age under 65	2,601	1.29	9.9	0.94
16 Alcohol- and drug-induced organic brain syndrome	2,249	1.23	9.2	0.91

[a]Source: Medicare Part A claims, Michigan, 1982.
[b]CV=coefficient of variation.

TABLE 8. Variation (R^2) in Hospital Costs and Length of Stay Explained by Alternative Classification Systems in Four States in 1982[a]

Variable and System	Percent of Variation Explained			
	Michigan	New Jersey	North Carolina	Washington
Hospital costs				
DRGs	3.9	3.6	3.6	5.3
Staging	5.7	5.9	5.7	10.5
CRGs	5.2	4.7	4.4	9.6
Length of stay				
DRGs	8.2	4.4	7.5	7.8
Staging	10.9	5.8	9.7	12.0
CRGs	11.2	5.4	8.4	12.3

[a]Source: Medicare Part A claims, 1982.

outliers, hospital location, the hospital's teaching status, etc. Only simulations of the complete PPS can show whether general hospitals would make or lose money on these patients. Such simulations are in fact the topic of one of the articles in this Special Section.

Nevertheless, the poor explanatory power of DRGs definitely weakens that system's credibility among providers (both the psychiatrists and the hospitals that treat these patients). More research is needed to develop a patient classification system that better discriminates among psychiatric patients on the basis of their resource use.

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Differences in Resource Use and Cost Among Facilities Treating Alcohol, Drug Abuse, and Mental Disorders: Implications for Design of a Prospective Payment System

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Specialized psychiatric facilities, including qualified distinct-part units in general hospitals, are exempt from Medicare's diagnosis-related group prospective payment system (PPS). One major reason for continuing the exemption is the redistribution of revenue that would probably occur if a single national price were established for care at the diverse facilities that treat patients with psychiatric and substance abuse disorders. This study investigated the extent of such potential redistribution in a private health insurance data base and found that a PPS would systematically underpay specialized facilities and systematically overpay general hospitals without specialized units. Alternatives for addressing this problem are discussed.

(Am J Psychiatry 1987; 144:616–620)

In its December 1985 report to Congress, the Health Care Financing Administration recommended that Medicare's prospective payment system (PPS) not be currently extended to include treatment in specialized psychiatric facilities and psychiatric units of general hospitals. Research sponsored by the Health Care Financing Administration, the National Institute of Mental Health (NIMH), APA, and other groups contributed to this conclusion. This paper reports on a portion of that research.

Much of the concern about applying the diagnosis-related group (DRG) PPS to the alcohol, drug abuse, and mental health (ADM) field stems from the revenue redistribution among different types of facilities that might result. The PPS determines payment on the basis of length of stay and cost averaging. General hospitals with "scatter beds," general hospitals with distinct-part units, private and public psychiatric hospitals, and free-standing and hospital-based substance abuse facilities all treat ADM disorders. When a DRG payment weight is based on an average length of stay for treatment occurring in all types of facilities, the resulting payment may be greater than cost for general hospitals with "scatter beds" and less than cost for specialized facilities. Steven Jencks has called this the problem of "fairness" in a PPS ("Implementing PPS for Psychiatric Inpatient Care: The Opportunities and the Challenge," presented at the annual meeting of the American Public Health Association, Anaheim, Calif., Nov. 13, 1984.) Others have referred to the "systematic risk" faced by specialized psychiatric facilities in a PPS (1). When there is systematic risk, a facility receives no protection from the law of large numbers, which is relied upon to equalize costs and revenues at a facility over time. If more costly patients are likely to be treated at specialized facilities, PPS payments based on an overall average will redistribute net revenues away from the specialty toward the nonspecialty sector. Moreover, systematic risk presents problems for patients as well as facilities. Financial incentives associated with this redistribution may affect patients' access to care, the treatment offered to ADM patients, and the financial viability of distinct-part units and specialized ADM facilities (1).

The large majority of Medicare's ADM admissions are to general hospitals (2). The potential in Medicare's PPS for redistribution between general hospitals with and general hospitals without distinct-part units has recently been analyzed (see the paper by Freiman et al. in this Special Section). Interest in the financial impacts of prospective payment extend, of course, beyond the Medicare system. Medicare itself is a relatively minor payer for most psychiatric facilities (2). However, the Health Care Financing Administration's policy toward prospective payment for ADM conditions may be viewed as a precedent by other payers. It is therefore critical to study—for payers other than Medicare and in settings including the full range of facilities that treat ADM disorders—the potential redistributive impact of prospective payment.

Taube et al. (3) studied samples of admissions from state and county mental hospitals, private psychiatric

Received April 30, 1986; revised Nov. 19, 1986; accepted Jan. 9, 1987. From the Health Data Institute, Inc., Lexington, Mass.; the Department of Economics, Boston University; the Harvard Medical School, Boston, Mass.; and the Michigan Health Care Education and Research Foundation, Detroit. Address reprint requests to Dr. McGuire, Department of Economics, Boston University, 270 Bay State Rd., Boston, MA 02215.

Supported by contract 278-84-0011(DB) from NIMH.

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hospitals, and general hospitals with psychiatric units. The median length of stay by facility was as follows: general hospital, 12.0 days; private psychiatric hospital, 19.4 days; public hospital, 27.1 days. The same study found that only a small portion of these differences in length of stay could be explained by case mix as measured by DRGs. Using a sample of discharge abstracts from 1977, Wallen (4) found that within broad diagnostic categories (e.g., neuroses, psychoses), patients treated in general hospitals without distinct-part units had shorter lengths of stay, received fewer psychotherapeutic services, and were more likely to be discharged to another facility than patients in other settings. The implication of these findings is that a DRG-based PPS would systematically redistribute revenues to facilities with shorter lengths of stay while decreasing revenues to facilities with longer lengths of stay.

This paper examines the potential redistributive financial impact of a PPS through analysis of claims from a single, large private health insurance carrier. Our data and analysis are of interest for several reasons. First, the admissions we studied came from the full spectrum of types of providers, including general hospitals, alcohol treatment facilities, and private psychiatric hospitals; only public hospitals were infrequently represented. Second, both charges and length of stay could be analyzed. Third, the insurance coverage and covered population were relatively homogeneous, which allowed us to rule out the hypothesis that differences in use among facilities are due to differences in insurance coverage or characteristics of patients.

METHOD

The data we used were for 29,602 admissions for inpatient care of psychiatric and substance abuse episodes during 1981 and 1982 reported on insurance claims submitted by employees and their dependents to a major Blue Cross and Blue Shield plan. In addition, claims for 1980–1983 were available, so we could create certain variables that described previous and subsequent inpatient treatment.

Physician claims paid by the same carrier were searched for the professional bills corresponding to the hospital admission. These claims were merged with the hospital claim to create a single record. Data elements for each physician claim included the physician provider identification code, provider specialty, procedure code, number of services, service date, and the charged and paid amounts. When professional services were included in the daily rate at a facility, there was no separate professional bill.

Data elements included a scrambled contract number, the birth year of the claimant, a relation code that indicated whether the patient was an employee or a dependent, the sex of adult claimants, discharge diagnosis, room/board and ancillary charges, total charges, admission and discharge dates, and hospital identification number. We went over the data several times to ensure that duplications, errors in coding, and other inaccuracies were removed. The episode files that we created included variables from hospital and physician claims and other sources.

Coverage for inpatient treatment of mental disorders, including substance abuse, was 45 days per benefit period. Admissions separated by less than 60 days were considered to be part of the same benefit period. There were no deductibles or coinsurance requirements for employees or dependents when they were admitted to participating hospitals. Psychiatric day or night care (when the patient was in the hospital for less than a continuous 24-hour period) was limited within the overall 45-day limit, with 2 days of day/night care counting as 1 full day of inpatient psychiatric care. All professional services were fully covered without limit when the patient was hospitalized.

Physician claims provided *ICD-9* diagnosis information, and the *ICD-9* codes were used to create DRGs 425–438. The hospital diagnosis was used when there was no physician claim (usually in a free-standing substance abuse facility). *ICD-9* codes were limited to four digits. Two DRGs were not included in this analysis: DRG 424 and 433. The episode claims that would have been assigned to DRG 424, psychiatric diagnosis with surgical procedure, were dropped from the data set because the admissions did not appear to be primarily for treatment of psychiatric disorders. DRG 433, substance abuse admissions discharged against medical advice, was not used because the data base did not support this distinction. It is likely, therefore, that DRGs 434–438 included some discharges against medical advice. Unclassified cases were dropped from analysis.

Cost included hospital room/board and ancillary costs. Charge data reported on claims were adjusted by a cost-to-charge ratio, supplied by the carrier, to determine cost. Length of stay was calculated from admission and discharge dates.

RESULTS

The average length of stay for all admissions was 17.64 days, at an average cost of $3,261.70. Cost and length of stay by DRG are shown in table 1. Three DRGs (425, 430, and 438) accounted for the majority of admissions. There was considerable variation in these resource use measures both across and within DRGs. As has been noted in several other studies, the coefficient of variation for both length of stay and cost within a DRG was about 100 (see the Freiman et al. paper in this Special Section and references 2, 3), implying that the standard deviation of cost and length of stay was about as large as the mean. This simple variance is not the source of systematic over- or underpayment to facilities. If patients were randomly distributed across facilities, no long-term losses or

TABLE 1. Mean Length of Stay and Cost by DRG for Inpatient Care of Psychiatric and Substance Abuse Episodes in 1981–1982[a]

Diagnosis-Related Group	N	Length of Stay		Total Cost of Hospital Stay	
		Mean (days)	CV[b]	Mean ($)	CV[b]
425 Acute adjustment reactions and disturbances of psychosocial dysfunction	1,925	17.62	98.0	3,378.08	92.0
426 Depressive neuroses	7,794	18.25	103.7	3,515.69	75.5
427 Neuroses except depressive	864	18.68	90.4	3,713.18	76.1
428 Disorders of personality and impulse control	431	19.44	117.6	3,660.08	90.2
429 Organic disturbances and mental retardation	1,649	24.78	57.9	5,288.40	61.9
430 Psychoses	5,882	20.26	74.8	3,488.87	87.6
431 Childhood mental disorders	287	33.91	78.2	5,325.00	89.4
432 Other diagnoses of mental disorders	59	11.05	118.8	2,519.33	126.0
434 Drug dependence	144	9.55	73.3	2,289.43	68.1
435 Drug use except dependence	47	10.06	105.8	2,271.56	100.7
436 Alcohol dependence	1,777	20.13	47.1	3,188.09	48.9
437 Alcohol use except dependence	110	4.34	166.1	1,289.40	162.1
438 Alcohol- and substance-induced organic mental syndrome	8,633	13.08	77.0	2,397.82	69.0
Total	29,602	17.64	88.5	3,261.70	81.7

[a]Source: claims to a major Blue Cross and Blue Shield plan.
[b]CV=coefficient of variation.

TABLE 2. Mean Length of Stay and Cost by Type of Facility for Inpatient Care of Psychiatric and Substance Abuse Episodes in 1981–1982[a]

Type of Facility	Total Number of Admissions	Mean Length of Stay (days)	Mean Cost ($)	Patients With Prior Admission (%)
General hospital without specialized unit	2,301	8.02	1,897	38.6
General hospital with specialized unit	13,042	15.71	3,380	31.3
Private psychiatric hospital	6,052	23.08	4,461	45.2
Public psychiatric hospital	1,244	28.07	691[b]	42.0
Free-standing substance abuse facility	2,399	21.75	2,618	21.3
Hospital-based substance abuse facility	4,564	15.76	3,061	44.0
Total	29,602	17.64	3,262	36.3

[a]Source: claims to a major Blue Cross and Blue Shield plan.
[b]This is only the amount paid by the carrier. It underestimates the cost.

gains could be expected. To examine the impact of a PPS on a type of facility, it is necessary to investigate how more costly and less costly patients are distributed across types of facilities.

Table 2 shows the average length of stay and cost by type of facility. Less than 10% of the admissions were to nonspecialized facilities. Admissions to these facilities had much lower average lengths of stay (8.02 days) and costs ($1,897) than other admissions. Admissions to private psychiatric hospitals and free-standing substance abuse facilities had longer average lengths of stay (23.08 and 21.75 days, respectively) than admissions to ADM units based in general hospitals (15.71 days). The average cost per day in these free-standing facilities was less, however, so the average total cost at a free-standing substance abuse facility ($2,618) was less than in a hospital-based facility ($3,061), even though the average length of stay was 6 days more. Cost figures for public facilities are regarded as unreliable, since charges by the facility and payment by the carrier are not closely related to actual treatment costs.

An understanding of the factors that lie behind differences in average resource use across facilities is critical for formulating a policy for prospective payment. Of most immediate concern is whether adjustment for case mix as measured by DRGs accounts for differences in average cost. Before examining this issue with these data, we report two possible sources of differences that are unavailable on many other data sets: the percentage of patients with a prior admission and the specialty of the treating physician.

For each of the 29,602 admissions in our data file, all prior admissions for up to 12 months before the admission date were identified. We were interested in whether facilities with longer lengths of stay or those with higher costs were treating patients who had been previously hospitalized for their illnesses. Prior admission might serve as a proxy for severity of illness or lack of response to treatment.

Table 2 shows the percentage of patients who had had a prior admission in the previous 12 months in each type of facility. These data do not show any clear relationship between the percentage of patients with a previous admission and the cost or length of stay. Excluding public hospitals, free-standing substance abuse facilities had both the smallest percentage of patients with prior admissions and a relatively high average length of stay. These findings may be due to the regular 28-day program offered to all patients and to a selective admissions policy. It is notable that

TABLE 3. Specialty of Physicians Receiving Highest Level of Payments for Inpatient Care of Psychiatric and Substance Abuse Episodes, by Type of Facility, in 1981–1982[a]

Physician's Specialty	Percent of Admissions[b]			
	General Hospital Without Specialized Unit (N=1,514)	General Hospital With Specialized Unit (N=8,674)	Private Psychiatric Hospital (N=4,001)	Hospital-Based Substance Abuse Facility (N=2,599)
Psychiatrist	13.9	69.0	89.6	27.1
General practitioner	22.7	6.2	0.3	25.3
Internist	30.0	15.8	3.8	23.3
Other	33.8	9.0	6.3	24.4

[a]Source: claims to a major Blue Cross and Blue Shield plan.
[b]Percents may not total 100 because of rounding.

FIGURE 1. Admissions to Different Types of Treatment Facilities for Substance Abuse and Psychiatric Disorders Treated by Psychiatrists and Nonpsychiatrists in 1981–1982

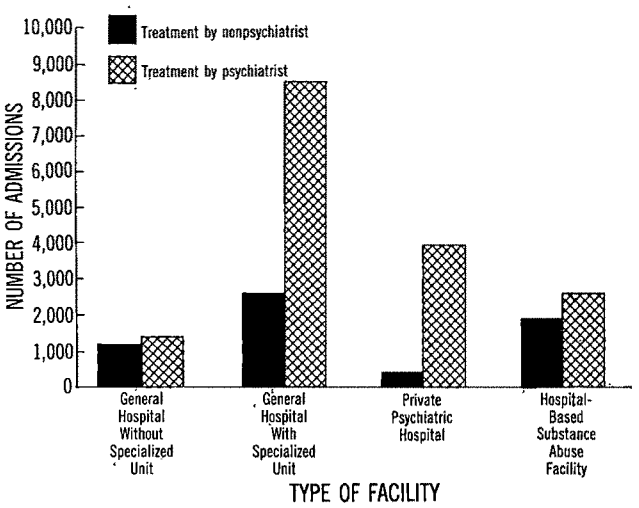
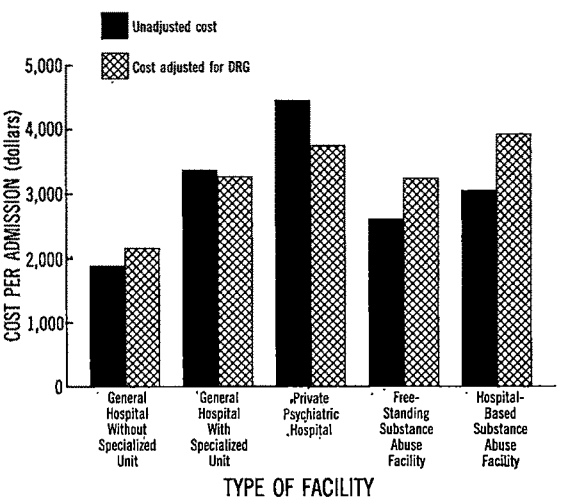


FIGURE 2. Unadjusted Costs and Costs Adjusted for DRGs of Admissions to Different Types of Treatment Facilities for Substance Abuse and Psychiatric Disorders in 1981–1982



hospitals without a specialized unit had about the same percentage of patients who had had a prior admission as did the more specialized facilities. General hospitals without psychiatric units appeared to be a regular site of care for some patients.

For the majority of admissions to general hospitals, private psychiatric hospitals, and hospital-based substance abuse facilities, physicians' bills were merged with facilities' claims. Facilities that included professional care in the daily rate had no merged physicians' bills. In total, 16,788 admissions included information from both the hospital's claim and the physicians' bills submitted during the inpatient episode.

Total payment to physicians during the admission was recorded, as well as the specialty of the physician receiving the highest level of payments. These data are shown in table 3 and displayed in figure 1. Psychiatrists treated almost 70% of the patients in general hospitals with specialized units and almost 90% of the patients in private psychiatric hospitals. However, psychiatrists were the primary physician (as defined by receiving the highest level of payment) for only about 14% of admissions to general hospitals without specialized units and only 27% of admissions to hospital-based substance abuse facilities. It is clear from these data that it is important to investigate type of physician as well as type of facility. Our findings raise the possibility that type of physician is the key to understanding why costs differ systematically across facilities. This issue is discussed in more detail by Morrison et al. (2).

To examine to what degree differences in average cost at different facilities could be accounted for by case mix as measured by DRGs, we used a regression model to estimate the average case-mix-adjusted cost at different types of facilities. The model was fitted by using admission as the unit of observation, with type of facility and DRG entered as dummy variables. The results are displayed in figure 2, which shows the unadjusted differences in average cost (from table 2) and the differences after case-mix adjustment. (Full regression model results are available in Morrison et al.'s report [2]). The adjustment amounts to asking what the average cost per admission would be if each type of facility treated a caseload with the same mix of DRGs. Differences in cost among types of facilities

after the adjustment are due to factors other than the mix of DRGs.

Differences in average cost are diminished by adjusting for the mix of DRGs. Thus, we found that some of the differences in average cost were due to case-mix differences as measured by DRGs. Some of the differences were not, however, and remained after adjustment. Private psychiatric hospitals and hospital-based substance abuse facilities had the highest adjusted cost per case. The most striking difference in figure 2 is between general hospitals without specialized units and all other facilities. The average cost at a general hospital without an ADM unit was at least $1,000 less than the average for other types of facilities, after adjustment for DRGs.

DISCUSSION

The main finding of the study is that a DRG-based PPS is likely to cause major redistribution of resources for treatment away from the more specialized facilities and toward those that are less specialized. The largest "winners" would be general hospitals without psychiatric units; the largest "losers" would be private psychiatric hospitals and hospital-based substance abuse facilities. The magnitude of redistributions could be substantial. Many facilities might lose or gain an average of several hundred dollars per patient. This level of financial impact can be expected to have major influences on the system of care. The present PPS provides for urban/rural differences, area wage rate differences, and special payments for teaching costs—adjustments that might moderate the redistributions we found. Adjustments for these factors, however, are not enough to eliminate major redistributions (2 and the paper by Freiman et al. in this Special Section).

If DRGs do not fully account for differences in expected resource costs for patients across facilities, a DRG-based PPS can lead to problems of access for patients and undermine the financial viability of specialized facilities' treatment programs. A facility cannot be expected to continue to absorb losses indefinitely. Access may be denied to certain patients, or levels of care may be dramatically cut back in order to maintain financial viability. There are a number of approaches for dealing with systematic gains or losses imposed by a PPS (see McGuire et al. [1]). One is to improve the classification system so as to better distinguish the more and less severely ill patients. Although this is an active area for current research, no potential improvements to DRGs have been widely tested or appear ready for incorporation in a classification system.

In the absence of sufficient improvements in the classification system, a second set of options associated with payment system redesign should be considered for addressing the fairness issue. One possibility is to calculate the prospective payment separately for types of facilities rather than averaging over all facilities. Payment to a psychiatric hospital would, for example, be determined by the average cost of treatment of patients in a DRG at similar facilities rather than the average of all facilities together. This would eliminate redistribution among types of facilities.

Other payment system options include calculating payment partly on the basis of cost during an admission. An enhanced outlier policy or a mixed system that combines elements of prospective and cost-based reimbursement would moderate redistribution both across and within types of facilities (5). These payment options are currently being explored in research sponsored by NIMH.

The analysis presented here draws attention to ADM patients treated by nonpsychiatric physicians in general hospitals without specialized ADM units. It is predominantly this group of patients whose costs differ from those of patients treated in specialized facilities. Although these patients may be classified in the same DRG as patients treated in specialized facilities, they may differ in important ways from other patients. Nonpsychiatric physicians may not refer to psychiatrists patients who tend to be less seriously ill (and less costly). Further investigation into which patients are treated in the general health sector and what care they are receiving is clearly warranted.

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Commentary

The Future of Psychiatry

Thomas Detre, M.D.

The author reviews the vicissitudes of psychiatry's history over the past 50 years and urges the profession to abandon false boundaries between mind and brain and to make a commitment to the scientific validation of prevailing theories of the etiology of psychiatric disorders. He argues that the separation of psychiatry and neurology is no longer justified. He calls instead for a carefully conceived new career path leading to specialization in clinical neuroscience and further urges that psychiatric training programs be restructured to focus on the critical examination of problem solving and validation methods.

(Am J Psychiatry 1987; 144:621–625)

Over the past 50 years, many articles and lectures and several largely unsuccessful commissions have attempted to deal with psychiatry's identity as an independent specialty. Perhaps because, as the late Mayer Gross claimed, the dysphorics are overrepresented, at least among academic psychiatrists, we believe that we are the only ones whose claim for unique competence is challenged by other disciplines. The facts, however, do not support our contention. The optometrists want an increasingly large share of the ophthalmologists' practice; podiatrists have invaded the territory that once belonged to orthopedists; gynecology, after it was almost eliminated by the discovery of antibiotics and the abdominal surgeons who wanted to cut out the same organs, is busily concentrating on problems of fertility; obstetrics is threatened by the midwives, who are ready to re-enter the delivery room; dentists and otorhinolaryngologists are locked in a deadly battle over the maxilla; hematologists and oncologists are after the same blood. And so it goes on, and it must go on. As science and technology advance, complex tasks are simplified and are gradually taken over by emerging new professions.

Undoubtedly, we were not passive bystanders either. Starting in the late 1930s, when neurosciences were still in their infancy, we discovered to our great relief that psychology and the social sciences contributed far more toward the understanding of our patients than did neurology. The decision to disaffiliate ourselves from neurology, however, set a historical precedent: we became the first medical specialty without ties to any organ or organ system.

One by-product of our nearly exclusive reliance on psychosocial explanatory theories was that we rid ourselves of problems that did not fit our newly found identity. We abandoned the epileptics, the demented, the developmentally disabled, and the retarded (1) and asked the police to take care of the alcoholics, the substance abusers, and the delinquents. We displayed great compassion by embracing the existentially unhappy and were ready to treat problems such as low self-esteem, failure to achieve one's creative potential, and chronic inability to trust. Soon we reached out again and enrolled a large group of people who were described by their friends, families, or employers as obnoxious, irritating, or uncooperative. Although by substituting such terms as passive-aggressive, narcissistic, and passive-dependent for less endearing ones such as pain-in-the-neck and s.o.b. we made a substantial contribution to good manners, we totally confused ourselves and the public about the meaning of mental illness.

Encouraged by the warm reception of the upper middle class and our growing influence, we performed the acrobatic act known as "Look, mom, no hands," explaining to the world that anybody, well almost anybody, could understand psychiatric disorders. All

Based on a lecture delivered to the Department of Psychiatry, Yale University School of Medicine, New Haven, Conn., on Jan. 4, 1985. Received Jan. 30, 1986; revised Sept. 2, 1986; accepted Oct. 20, 1986. From the University of Pittsburgh, Health Sciences. Address reprint requests to Dr. Detre, Health Sciences, University of Pittsburgh, 3811 O'Hara St., Pittsburgh, PA 15213.

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that was required was a bit of intuition and an appreciation of the oppressive forces operating in our families and society at large. Having convinced ourselves that cure could be achieved only with intensive psychotherapy, which regrettably few people could afford, we decided that overcoming social and economic inequities must receive the highest priority. We should take legitimate pride in our successful campaign, which improved access to psychiatric care for the poor and disenfranchised. Unfortunately, however, the method chosen to achieve this otherwise noble goal—the establishment of community mental health centers—further legitimized the separation between psychiatric care and general health care.

This Weltanschauung, as it turned out, was in perfect tune with the spirit of the early 1960s and led to one of the oddest alliances yet conceived: that among clinical psychiatry, community psychiatry, and psychoanalysis. Together we wrote a splendid script on the psychological society. We were so successful that our ranks were gradually swollen by an increasingly varied group which, in addition to health professionals, social workers, and psychologists, included streetologists, faith healers, and experts in both dressed-up and naked encounter groups, all of whom declared their undying commitment to promote the mental health of people in the United States (2). Crowning our spectacular achievement were two savvy political decisions: we abolished double specialty boards in psychiatry and neurology and concluded that internship was an unnecessary preparatory step for specialty training in psychiatry. These decisions, based on an extraordinary lack of foresight, were very costly. During this phase of our history, while we managed almost totally to demolish traditional asylums, we paradoxically made our specialty an asylum for physicians who were running away from medicine.

OUR RETURN TO MEDICINE, HAT IN HAND

Finally, in the 1970s, we began to reverse ourselves. The internship program was reinstituted. Training in neurology was encouraged. A few of our leaders even went so far as to declare psychiatry to be a primary care medical specialty. The department of psychiatry at Washington University, which under the leadership of Eli Robins continued to maintain its commitment to nosologic research, suddenly acquired new respectability. Several departments, after apologizing to the residents for taking time away from psychotherapy supervision, started to teach psychopharmacology. Concerted efforts were also made to reconquer lost territory. Our sudden fascination with the aged, the demented, and the developmentally disabled, however, did not engender much enthusiasm. Having serviced them for many years, special educators, psychologists, pediatricians, and a new brand of neurologists called behavioral neurologists became quite rude, insisting that they had legitimate claims to these patients. Alcohol and substance abusers also protested; they informed us that they had finally learned what we had taught them and no longer believed that their problems should be considered the domain of psychiatrists.

Our having come up with many new and not necessarily well-conceptualized theories about the etiology and treatment of psychiatric disorders throughout our relatively short history is not surprising. What is astounding is how little effort has been made to test the validity of our theories and how long we have remained a shelter for bankrupt ideas. Undoubtedly, what appears solely as evidence of our gullibility is also a product of complex sociopolitical interactions. Psychoanalysis in the United States, for example, found a fertile nest in military psychiatry during World War II. The seemingly powerful effect that psychological interventions had on soldiers who, instead of being sent home, were successfully treated for acute stress disorders near the combat zone convinced even the most skeptical of us that the prescription worked. The fact that nobody bothered to determine whether the supportive setting and the expectation for recovery alone could have done the trick is not surprising, inasmuch as randomized clinical trials were not yet in fashion. But other treatments—CO_2 inhalation, insulin coma, psychosurgery, narcoanalysis, electronarcosis, and LSD treatment, for example—continued to survive long after their lack of effectiveness had been convincingly demonstrated. Nor did the dramatic response produced by pharmacotherapy on the bewildering array of manifestations observed in schizophrenia have an unsettling effect on those who prefer to interpret each of the symptoms separately, having persuaded themselves long ago about the psychological origins of this devastating illness.

INTELLECTUAL EQUIVALENT OF DISNEYLAND

Although the unsound reasoning that underlies many of our assumptions about mental illness tends to be justified by the alleged inevitability of the mind–body dualism, nothing is further from the truth. The source of the confusion is that while the "mind" and mental functions constitute a legitimate and convenient conceptual framework to describe certain phenomena about psychiatric illness, it is not an avenue for the generation of biological theories by which we can deduce from the nature of mental defect its etiology and pathogenesis. If, on the other hand, mental illness and the attendant psychological symptoms are not regarded as expressions of as yet undefined disorders of the central nervous system (or another organ system) but disorders of the mind, then one graceful leap will lead us to conclude that the pathological state can be defined only by the symptoms it produces (3). Having extricated the mind, so to speak, we further embellished this rather remarkable spiritual construct

by misusing the term "functional" to mean "psychogenic," when, in medicine, it is intended to convey impaired functioning of a system. In doing so, we created the intellectual equivalent of Disneyland: We can go on our speculative excursions, confident that we will always come back to where we began. We continue to be spellbound by the variety of acute and chronic stresses that impinge on our lives without the distracting thought that characteristics of the organism's processing and responding to such events may be as important as or more important than the so-called specificity of the stress itself.

In other words, even though persistent or progressive deficits in adaptation following stress, including secondary developments of a compensatory nature, may appear as purely psychological phenomena, such changes, by definition, must be the products of altered functioning of the organism. The history of medicine is replete with examples demonstrating that our failure to detect changes in the functioning or structure of organs or organ systems proves only the limitations in our diagnostic methodology and cannot be construed as evidence for the psychological origin of etiology or pathogenesis.

Our failure to appreciate the limits of the data and the nature of the evidence continues to play havoc with us. When it once again became fashionable to think now and then about the brain, we were less interested in the implications of new knowledge than with the application of emerging findings from neurobiologic research to support as yet unproven hypotheses derived from psychoanalysis. The nomination of the unsuspecting corpus callosum as the potential site for the unconscious and attempts to link uncritically what little is known about the neurophysiology of sleep with Freud's theory of dreaming are examples of this kind of endeavor (4). We also seem to forget that our current nosologic system, *DSM-III*, is still on a very narrow foundation. Given that the diagnoses are based primarily on what the patient complains about, how long the patient has been complaining, and how much the patient is complaining, using treatment response alone to prove their existence leads to mischievous conclusions.

We do not have to feel lonely in our disarray, however: our half-sibling and our stepmother, psychology and neurology, respectively, are also engaged in an exercise of self-appraisal. In a 1980 article entitled "Whither Psychology?" Davies and Wetherick (5) lament, "[Ever since psychology became independent of philosophy] at no time has it been clear, even to its practitioners, what constituted the boundaries of the discipline. Within the ranks of psychologists ... fragmentation into schools occurred. On the whole, it was agreed, not without argument, that the new science was to be modeled on the methods of the relatively mature nineteenth century sciences of physics and chemistry: observation, prediction, and experimentation. Psychology was to be based upon empiricism. This has produced a mass of data based on controlled observation, however, this is not in itself an adequate basis for any science."

What has been said about psychology to some extent also applies to psychiatry and—as will become clear—to neurology as well. In a 1984 editorial suitably entitled "Whither Neurology?" Martin (6) expresses concerns that future neurologists are denied "the skills that would make them most useful to society." He complains about the decreasing number of neurologists choosing research training and believes that many applicants entering the field have questionable credentials, insufficient training in internal medicine, and limited exposure to neurosciences, causing residents to believe that such knowledge is irrelevant to clinical problems in neurology. He suggests that these deficiencies can be remedied by requiring that those interested in clinical careers spend at least 2 to 3 years in internal medicine before specializing in neurology, while those interested in research, unless they are graduates of M.D./Ph.D. programs with majors in neurosciences, spend several years in basic science research. Martin defines the responsibility of neurology as "the diagnosis and management of any disorder in which the involvement of the central nervous system is included in the differential diagnosis ... [which could, if the neurologist is interested, encompass] the diagnosis and management of disorders affecting behavior."

TERRITORIAL IMPERATIVE

You may wish to register a complaint about the territorial aspirations of neurology. I submit to you, however, that the problem is not the lack of a clear boundary between neurology and psychiatry. Even though neurology, unlike psychiatry, always remained in the mainstream of medicine, neither discipline has been or is currently providing training that will provide the necessary competencies for patient care. Although exposure to neurology is a requirement for Board certification for psychiatrists, the experience provided is often perfunctory. Much the same can be said for the psychiatric training of neurologists. During the last 10 years both psychiatry and neurology have gone down the road with various more or less successful Scotch-taping measures to strengthen their scientific underpinnings. Both have recruited Ph.D.s, hoping that their methodologic expertise will somehow infuse the medical troops with the required sophistication to conduct research. Moreover, neurology, until it gave birth to a somewhat ill-conceived subspecialty called behavioral neurology, showed little interest in psychopathology, limiting itself primarily to the study of aphasia, apraxia, and agnosia and calling upon its equally uninformed colleagues from psychiatry to take care of clinical problems that were too tedious to handle.

Psychiatry, on the other hand, in an attempt to cope with its expanding responsibilities vis-à-vis the aged

and the developmentally disabled, populated its departments with neuropsychologists and also managed to lure away a few disenchanted neurologists who were interested in behavior. Specialty training in psychiatry and neurology now includes some exposure to clinical pharmacology, but neither discipline has sufficient knowledge of how the pathophysiology and treatment of various disorders affect the functioning of the nervous system. Recent advances in neurochemistry, neuroendocrinology, and computer-assisted electrophysiologic and imaging methods, for example, should have acted as a major impetus for the investigation of various encephalopathies and the attendant changes in mental functioning, but this is not happening.

TOWARD A CAREER IN CLINICAL NEUROSCIENCE

The real problem, and we might as well face up to it, is that if neurology and psychiatry are each involved in the study and care of disorders of the central nervous system, a position toward which both specialties seem to be inching, then the continued separation of neurology and psychiatry is no longer justified.

In my opinion, the only viable solution is a new career path leading to specialization in what, for lack of a better term, I would call clinical neuroscience. It should be concerned with disorders of the nervous system, regardless of whether the etiology of the disorder is known or unknown or whether the disorder is primary or secondary. Trainees should have adequate exposure to medicine, neurology, psychiatry, and pharmacology and be taught what neuropsychology, electrophysiology, and imaging methods can contribute to the assessment of brain functioning in living patients. Although training in neurosciences is important, acquisition of basic skills in epidemiology and biostatistics is no less significant. We must admit that the time for renaissance doctors who know everything about everything has long passed. Subspecialization in an area of choice, be it developmental disorders, metabolic encephalopathies, aging, neuromuscular disorders, so-called functional psychoses, or whatever, should follow an integrated and carefully thought-out curriculum in medicine, neurology, and psychiatry, which could take approximately 5 years. Armed with such knowledge, we could make a substantial contribution to patient care, allowing us to relinquish our role as social pseudoscientists on semipermanent vacation from medicine.

Research training, as Martin (6) has suggested, should follow clinical training and be tailor-made to suit the trainee's needs. Regardless of whether the career choice will involve patient care, clinical investigation, or laboratory science, the emphasis throughout training should be on the critical examination of problem solving and validation methods both to prepare young physicians to handle the explosion of new information and to protect them from the embarrassing mistakes our generation has made. In other words, what is being taught and for how long is less important than how the subject matter is presented and by whom. We can no longer rely only on clinician-educators. Clinical skills should be taught by active investigators, who by doing research have a clear appreciation that today's facts are merely way stations and should be taken seriously only until new findings have modified them or rendered them valueless.

Failure to achieve what one might broadly call psychosocial competence in our trainees, however, would merely create another kind of reductionism, replacing the brainless with the mindless approach to clinical problems. There is increasing recognition that much of what is now taught to psychiatric residents should become an integral part of the medical school curriculum. What Eisenberg (7) calls the "sociobiologic process of becoming ill, being ill, and getting well," what social anthropology can teach us about patienthood and illness, and what political science contributes toward the understanding of health care delivery systems properly belong in graduate medical education and should be learned by all physicians (8). I do not believe that any specialty should be given the sole responsibility and the priestly duty to become an expert and proselytizer of interviewing techniques or psychotherapy. Every physician must learn how to gather data that are critical for diagnostic and treatment decisions and to do so in a way that is vigorous and precise without being relentless or insensitive and, for that matter, without pretending that all encounters between patient and doctor are or should be therapeutic. Last but not least, all physicians, whether they are engaged in research or clinical care, should be trained to become practitioners of the informed consent doctrine. Discussing with our patients the pros and cons of various diagnostic and treatment options is not just a moral obligation but a major contribution to our own education. The very process makes it mandatory for us to acknowledge how limited our information is, encouraging us to behave modestly. Familiarity with the principles of informed consent will also help physicians to come to grips with the peculiar fact that the only difference between clinical practice and clinical research is that the latter is controlled while the former is not.

WHITHER CLINICAL FREEDOM?

There are other issues requiring our attention. Quite bluntly, we live in an increasingly cost-conscious world which insists that we provide something of value for the money. In doing so, we have entered a new era that has aptly been described as "the end of clinical freedom" (9). Oracular statements by senior clinicians regarding the efficacy of diagnostic methods or treatments will no longer be acceptable. Our diagnostic and treatment methods will have to be evaluated by rigorously controlled clinical trials. To meet the challenges,

we must do more than tinker with our traditional curriculum. Indeed, I doubt that any changes in curriculum, including the drastic ones I have proposed, will suffice. I agree with Ellard (10) that the best remedy, at least for the leading academic departments, is to strive for unabashed elitism by raising standards and "trading numbers for prestige."

Before closing, I might as well admit that my views find little support in psychiatric circles. Many still believe that our crisis is nothing more than a temporary halt in our final triumph. All we need is to assert ourselves and stop the other disciplines in their efforts to deplete even further the reservoir of "desirable" patients. Repeating with great conviction that we are physicians and thus absolutely anything we do is medical is one way to implement this scenario (11). Others think that dealing with noncompliant medical patients by using family therapy and behavior modification, perhaps even becoming primary care givers by getting acquainted with the management of one or two nonpsychiatric conditions, would be consistent with our aspirations to fulfill our mission (12). A more modest view is that the psychiatrist of the future will be restricted to providing "secondary and tertiary care for complex and difficult cases, whether the patients require psychoanalytic psychotherapy, pharmacotherapy, or environmental manipulation" (13). Regrettably, however, there is little evidence that competence in interpersonal relationships is something that psychiatrists are uniquely trained for or should be; thus, such skills have limited value for assuring our survival (14).

Last, there is what one might call the moral argument put forth to preserve psychiatry "as is," it being the only specialty that really cares about the patient as a whole. Frustrated patients, their families, legislators, and television talk show hosts all seem to agree that the humane touch is increasingly absent from the practice of medicine. This rising public outrage has led to vast curriculum changes in several reputable medical schools, the purpose of which is to counter the allegedly dehumanizing influence of our education and make us more responsive to our patients' psychological needs. All this sounds quite wonderful, but there are a few small problems that might abort our efforts to achieve personalized care. The first is economic: remuneration for patient care in the United States is inversely proportional to the amount of time a physician spends in direct personal contact with the patient. Thus, the income of high technology, surgical, and so-called hospital-based specialists is rising while the income of internists, pediatricians, and psychiatrists is steadily declining. The second minor problem has to do with the selection process. To be sure, premed students often have something touchingly caring listed among their extracurricular activities. Those who are ultimately chosen to enter our sacred order, however, continue to be the ones who have quantitative skills and high marks in science. I could go on, but it would not be productive.

I do not think any of these options are viable, but then again I must also be prepared to entertain the possibility that I am wrong. In fact, all of us who live long enough to see what we will be doing in the next century should be fully prepared for a disappointment. The chances that everyone's predictions will turn out to be wrong are overwhelmingly high. We already know that we educated too many physicians and built too many hospitals for tuberculotic and psychiatric patients. Our forecasts about traffic density, which guided plans for the size of highways and airports, our manpower and energy need projections, were all way off. In the meantime, new commissions are still being formed to study the future practice of health care in this country at great expense to the taxpayer. These commissions may come up with new buzzwords that make for stirring speeches at medical conventions, but usually they fall far short of solutions.

I end, then, where I began, preferring to fall back on the comfort of my own predictions than to trust those of someone else. As we learn from ever more persuasive evidence that the mind and the brain are one and the same, we must, as a specialty intent on evolving in a way that assures survival, abandon the false boundaries we have established in our game of king of the mountain with other medical and health care disciplines. Our new strategy should be a decisive move, carefully conceived, meticulously executed, and dedicated to providing clinical and research training to create a new breed of psychiatrists who are truly neuroscientists.

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Are Specialized Psychiatric Services Worth the Higher Cost?

Recent changes in health care financing policy have complicated the discriminatory pattern of third-party payment for psychiatric care. Until recently there was no need to account for the predictors of the cost of care or variations among providers in patterns of practice. In the past, researchers investigated the delivery of services, motivated by a fascination with the dynamics of a system rather than by a search for a formula for financial survival. Although the spotlight shines brightly on this area of research because of its currency in the debate about prospective payment, the central question is of long-lasting importance: What explains variations in the cost of psychiatric services?

The study reported by Mitchell and her colleagues in the Special Section in this issue joins a growing list of studies (1–3) which demonstrate that diagnosis does not predict the use of hospital resources by patients with mental disorders. None of the available case-mix measures based on diagnosis (e.g., diagnosis-related groups [DRGs], clinically related groups, or disease staging) hold much promise for use in a prospective payment system. The few measures, such as Horn's Psychiatric Severity of Illness index (4), that predict resource use more adequately have limitations in their applicability to payment systems. Variables other than diagnosis, however, are associated with variations in resource use. Mitchell et al. and Freiman and his collaborators (also reporting in the Special Section) found dramatic state-to-state variations in the cost of psychiatric hospital care. In the third paper in the Special Section, McGuire and his colleagues, like Freiman et al. and Taube and his co-workers (5), report on the higher average cost of psychiatric care in hospitals with specialized psychiatric services, such as inpatient units, than in general hospitals without specialized services, especially those which are not exempt from Medicare's prospective payment system. As noted by Mitchell et al., specific procedures in the substance abuse area, such as rehabilitation therapy and detoxification, also predict costs that are higher than those for symptomatic treatment (6). Finally, McGuire et al.'s study determined that psychiatric hospital services are more costly when provided by a psychiatrist than when provided by a nonpsychiatrist. These findings all suggest that specialized psychiatric services cost more: Higher costs are associated with specialized procedures, with treatment in certain states, with specialized psychiatric settings, and with services provided by a psychiatrist, even when costs are adjusted for case mix (e.g., by DRGs) or for some other presumed measure of increased need for treatment resources, such as readmission status.

Observing these differences in patterns of clinical practice, researchers and policy makers ask, What is the source of this variability? Is it a difference in efficiency? Is it a difference in the characteristics of patients in each of these settings, a difference unmeasured by DRGs or other case-mix or clinical measures of resource need? Or is it a difference in the role played by certain specialist providers in a functionally differentiated system of care, related in part to the needs of patients and in part to the needs of providers? Ideally, differences due to increased efficacy and efficiency or related to unmeasured patient need should be compensated in the payment system.

If specialization is the key to explaining the variation in the cost of psychiatric hospital services, then the next critical question emerges: Are specialized psychiatric services worth the higher cost, and can the higher cost be sustained? This line of

inquiry challenges research as it raises the eyebrows of policy makers and enflames the field of psychiatry.

The findings of the investigations reported in this issue of the *Journal* suggest a future direction for research and policy formulation. It is incumbent upon the field to refine the hypotheses and to help explain the variations in cost among certain providers in some states. Economists and health services researchers need the collaboration and cooperation of clinicians and administrators (as illustrated by these excellent papers). Policy makers need to have the findings explained and placed in context.

We believe that further research and reflection will discover that a proportion of the higher costs for specialized psychiatric hospital care are justified on the basis of patient need and that variables related to specialization can and should be incorporated into mechanisms for financing psychiatric services. We also believe, however, that there is a proportion of the cost that is due to inefficiency, as has been shown in general medicine and surgery (7).

It seems likely that while some of the variation in cost among states is due to patterns of practice based on provider preference, much of the variation may be due to the differential use of specialized services in one state in comparison with another. For example, the system of general hospital psychiatric care in some states may assume many of the responsibilities of state-operated psychiatric hospitals, resulting in longer and more costly stays by severely ill inpatients. In other states, the state mental hospitals may assume the burden for the more costly patients. State-to-state variations in the availability of insurance resources for psychiatric hospital care probably also influence the cost of care in various settings. Although not directly related to patient need, such variability affects the availability of and access to needed services for patients and should be accommodated in a payment system. Adjusting payments on a state-by-state basis and developing a measure to adjust for differences in the use of psychiatric services at the state level are potential policy options (8, 9).

Is the higher cost of specialized psychiatric services warranted? The patients treated by psychiatrists in specialty settings are presumed to be more impaired than those treated by nonpsychiatrists in general medical settings, and specialized treatments are expected to be more effective. We suspect that further research will sustain these assertions, justifying the higher costs. Research already suggests that undertreatment is to be feared as much as overpayment (10) and that short-run savings from prospective payment may be offset by subsequent increases in cost (11). Inadequate treatment, stemming in part from insurance limitations (12), may cause increases in indirect costs to society as well as increases in direct costs for services. More information is needed on the differential cost effectiveness of specific psychiatric treatments. This research, however, should be conducted in the same context as studies comparing medical and surgical treatment of cholecystitis or coronary artery disease.

In the end, when the impact of payment systems on the cost of care is assessed, it will be critically important to be able to distinguish efficiency from undertreatment. We must know whether a decrease in direct cost is accompanied by a clinically significant decline in the quality of care and a concomitant increase in direct costs due to continued impairment. These are the most important questions for the immediate future. Answering these questions will require collaborative policy research, informed by economists and other social scientists, psychiatrists, and policy makers joined in the study of the mental health service system. Only an informed profession can assess the data and the policy choices. We need more attention to quality research in this important area, as provided by this month's Special Section of the *Journal*.

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The Family History in Clinical Psychiatric Practice

Because the family history of psychiatric illnesses can be a powerful diagnostic aid and guide to treatment for individual patients, Baker et al., in this issue, evaluate practical alternatives for obtaining clinically useful family histories for hospital psychiatric inpatients. Their data demonstrate that methodically asking specific questions about each relative in the pedigree, generation by generation, yields much more clinically useful information than the less structured format used by most physicians. Baker et al. did not themselves evaluate the accuracy of diagnoses based on anecdotal information provided about other family members but cite previous studies in which diagnoses based on such family histories agreed well enough with those derived from direct examinations of relatives. On the basis of their findings, Baker et al. make easily implemented suggestions that would improve the care of many patients.

Who should be responsible for compiling the family history for psychiatric patients? A clinically experienced and specifically trained social worker took the informative family histories analyzed by Baker et al. Although they did not evaluate interviewer alternatives, a nurse with specialized training or a genetic counselor would undoubtedly do as well. An interactive computer program that could compile many of the pedigree details might reduce the effort required from professional staff.

Rigorously recording a sufficiently detailed family psychiatric history is unlikely to cost more than $200. It is important to remember that a comprehensive and accurate

family history need be taken only once for each patient. The average benefits, measured through reduced hospitalization costs or through the improved quality of life and productivity of the patient, will greatly exceed the measured costs of providing this service.

Although the usefulness and practicality of a detailed anecdotal family history have been demonstrated, such a history is not the "gold standard" in making genetic psychiatric diagnoses. There are times when it may be necessary to collect and review the diagnostic and treatment outcome information in the medical records of family members with psychiatric illnesses. Although systematic collection of medical data from relatives is unusual in psychiatric settings, it is customary in genetic counseling and should probably be done more often for psychiatric patients. For critical clinical decisions, direct examination of selected relatives may provide valuable additional information, although the logistical difficulties associated with obtaining the required cooperation from relatives restrict this approach to selected clinical and research settings. In most cases, implementation of the Baker et al. recommendations alone would lead to a significant improvement in patient care.

Whenever clinical or laboratory techniques are used to identify persons with an elevated genetic risk of psychiatric illness, there is the potential for damage to self-esteem or for causing the loss of insurability, employability, or apparent suitability as a reproductive partner. This potential harm must be minimized by our awareness and professional sensitivity in the collection and interpretation of family or genetic data and must be weighed against the clearcut benefits of more accurate diagnosis and treatment. There is no turning back the tide of growing scientific and lay awareness that genes do predispose to psychiatric illness, but our enthusiasm for the short- and long-term benefits of this burgeoning technology must not blind us to the possibility of unfortunate consequences for some individuals.

Eventually, by analyzing the DNA of patients, direct identification of the genes that predispose to psychiatric illnesses will be the most useful guide to accurate diagnosis. Clinical studies that use molecular genetic techniques to identify these genes will be difficult given that there are likely to be many such genes and that complex gene-environment interactions are probably responsible for most psychiatric illnesses. While waiting for the full elucidation of the genetic-metabolic basis of psychiatric illnesses, it is important that patients benefit now from the genetic information that is available through a sufficiently detailed and methodical family history.

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Family Diagnoses Missed on a Clinical Inpatient Service

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Methods for taking family psychiatric histories have been developed primarily for research rather than clinical settings. The authors compared family histories obtained independently by a research team and by PGY-3 residents on 52 consecutively admitted adult psychiatric inpatients. In contrast to the residents, the research team used a family tree, screening questions, and a structured interview based on diagnostic criteria and identified more than four times as many diagnoses in relatives as did the residents. The results demonstrate that a family history strategy derived from research methodology significantly enhances the gathering of important diagnostic information in a clinical inpatient setting.
(Am J Psychiatry 1987; 144:630–632)

A family psychiatric history is a crucial aid in diagnosis and treatment. With the increasing recognition that present symptoms are not specific enough to make accurate diagnostic distinctions in many illnesses, it has become particularly important. For example, in an acutely ill patient, psychotic symptoms alone cannot distinguish mania from schizophrenia (1). The use of a family history along with other data (e.g., course, premorbid history) decreases the misdiagnosis of bipolar patients as schizophrenic (1). This is also true for depression. Diagnostic criteria alone may fail to identify some patients with endogenous illnesses (2). A family history that includes major depression and response to a specific medication suggests both the diagnosis and preferred pharmacologic management of the patient (3–5). In addition, the family history is central to genetic counseling and education of patients' families about the risk of developing psychiatric illness (6, 7).

Although the family psychiatric history has such broad applications in psychiatric practice, little is known about the usefulness of common clinical interviewing techniques in detecting mental illnesses in the relatives of patients. Efforts to clarify the sensitivity and specificity of family history methods have concentrated on applications to research (3, 8–15). In that context, family history methods, in which diagnoses of relatives are made indirectly by use of one or more informants, have been compared to the family study method, in which diagnoses are made by direct interview of relatives. We now compare two approaches to taking and interpreting a family history in a clinical setting.

METHOD

Fifty-two patients admitted consecutively to Colorado Psychiatric Hospital consented to participate in the study as index cases. Diagnostically, they were a diverse group with a significant degree of substance use and psychotic and affective disorders (table 1). The patients were treated by PGY-3 psychiatric residents supervised by an attending psychiatrist. Each patient in the study had family histories taken by both a resident, as part of the required data base, and by the research team. The residents were blind to the research methods and goals.

Family histories were collected for the research team by a social worker with 14 years of inpatient experience. Using the patient and one relative as informants, the social worker drew a family tree including all first- and second-degree relatives. Although previous re-

Presented at the 138th annual meeting of the American Psychiatric Association, Dallas, May 18–24, 1985. Received Jan. 17, 1986; revised July 17, 1986; accepted Nov. 5, 1986. From the Department of Psychiatry, University of Colorado Health Sciences Center. Address reprint requests to Dr. Baker, Department of Psychiatry, University of Colorado Health Sciences Center, 4200 East 9th Ave., C-268, Denver, CO 80262.

The authors thank the CPH Blue Team residents and nursing staff for their excellent patient care, Dr. Robert Freedman for editorial assistance, and Annette Ginnane for manuscript preparation.

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TABLE 1. Primary *DSM-III* Axis I Diagnoses of 52 Consecutive Psychiatric Inpatients[a]

Diagnosis	N	%
Organic mental disorder	3	5.8
Substance use disorder	4	7.7
Schizophrenic disorder	9	17.3
Schizoaffective disorder	1	1.9
Atypical psychosis	3	5.8
Bipolar disorder	6	11.5
Major depression	14	26.9
Other affective disorder	3	5.8
Adjustment disorder	7	13.5
Other	2	3.8

[a]Total number of patients with substance use disorder as primary or secondary diagnosis=24 (46.2%).

TABLE 2. FH-RDC Diagnoses for 195 Relatives of 52 Psychiatric Inpatients Based on Research Team Methods and Residents' Methods

	Number of Diagnoses	
Diagnosis	Research Methods	Residents' Methods
Chronic schizophrenia	5	0
Schizoaffective disorder	1	0
Unspecified functional psychosis	3	0
Manic disorder	1	0
Bipolar disorder	5	1
Recurrent unipolar disorder	8	0
Depressive disorder	46	8
Alcoholism	103	18
Drug abuse	21	6
Senile organic brain syndrome	5	0
Other psychiatric disorder	37	4

search (3, 8–15) has for the most part been restricted to first-degree relatives, we chose to include second-degree relatives because we have observed that this is routine clinical practice. A few third-degree relatives were included when informants mentioned them spontaneously in the course of an interview. For 14 (27%) of the patients, a second informant was not available.

To help the informants quickly identify any relatives on the family tree who might have psychopathology, we administered a 12-item screening questionnaire based on the Family History Research Diagnostic Criteria (FH-RDC) (16) that listed symptoms of schizophrenia, mania, major depression, organic brain syndrome, and substance abuse. This screening identified 230 relatives for the whole patient group who had one or more of the 12 symptoms. We then asked the informants more questions about these relatives using a structured interview based on FH-RDC to determine the diagnosis.

Final FH-RDC diagnoses of relatives were made using these data by the attending psychiatrist and a second psychiatrist, who was unfamiliar with either informant. The concordance rate for diagnoses between the two Board-certified psychiatrists was 87%.

The two psychiatrists then independently reviewed the family data collected and recorded in patients' charts by PGY-3 residents. All patients had been discharged by the time of this review. The psychiatrists made FH-RDC diagnoses for relatives on the basis of the residents' chart information with a concordance rate of 90%. All diagnostic disagreements were resolved by discussion.

Finally, 16 of the PGY-3 residents who had admitted patients during the time of the study completed a questionnaire asking them to estimate how often they used various family history methods in their clinical practice.

RESULTS

The research team diagnosed 195 relatives using data they had acquired with structured interviewing methods. (The number of diagnoses, shown in table 2, exceeds the number of relatives because of relatives with multiple illnesses.) Only 35 of the relatives could be diagnosed on the basis of data obtained by residents, which were frequently insufficient to meet criteria for any FH-RDC diagnosis. This situation occurred for 24 additional relatives on whom data had been collected by residents, or over 40% of the 59 relatives for whom there was information in the charts. In contrast, only 35 relatives, or 15% of the 230 relatives who were the subject of a structured interview given by the research team, had information suggestive of a psychiatric disorder but insufficient for an FH-RDC diagnosis.

Of the six most severe psychotic and affective illness types (the first six listed in table 2), 23 diagnoses were made by research methods, whereas only one diagnosis could be made on the basis of information obtained by residents. Of the 23 research diagnoses, 12 were missed entirely by the residents, and 10 were not made owing to insufficient data listed in the charts. For example, a relative listed in the chart as "mental break" was diagnosed with chronic schizophrenia on the basis of information obtained by research methods. Another relative listed in the chart as "abusive; locked patient in closet" was diagnosed with recurrent unipolar disorder using research methods. Conversely, on a few occasions, the residents listed a severe psychiatric diagnosis in the chart without documenting supporting criteria. In each instance, the diagnosis could not be confirmed on the basis of data obtained by research methods.

In almost all cases, both the residents and the research team asked one screening question: whether or not relatives had a history of psychiatric treatment or hospitalization. Using a family tree in conjunction with that one question, the research team identified almost three times (62 versus 21) as many relatives as did the residents, who rarely used a family tree. Ten of 16 residents never used a family tree, and five others employed this method rarely or in less than half of their cases. Although 14 of 16 residents always asked their informants whether or not any relatives had had

psychiatric treatment or been hospitalized, the residents did not otherwise systematically or thoroughly ask questions about relatives using defined diagnostic criteria (e.g., FH-RDC was not used by any of the residents). Questions about depression, psychosis, or other symptoms were not asked unless the family information was thought to be pertinent to the patient's diagnosis. About half of the residents used a second informant.

DISCUSSION

The results of this study demonstrate that a family history method adapted from a simple research strategy significantly enhances the ability to diagnose major psychiatric disorders in relatives of patients in a clinical setting. Although the methods used by the research team required 30–90 minutes of interviewing time, they elicited crucial information for patients who were diagnostically complicated. Assigning a member of the treatment team to specialize in these techniques minimized the time spent by the psychiatrist for this task while increasing accuracy.

The results suggest that construction of a family tree greatly increases the sensitivity of screening questions about psychiatric symptoms or treatment. Thompson et al. (17) have suggested that the family tree provides more certainty about the relatives who come to the informant's mind. We have found that the informant may not spontaneously remember relatives with whom they have had distant or unpleasant relationships. In addition, anxiety about mental illness may cause the informant to forget or omit family members with a psychiatric diagnosis. For example, one patient repeatedly denied mental illness in relatives only to tell us after several weeks of hospitalization that his sister was treated with lithium. This obfuscation may also be due to a lack of familiarity with the meaning and significance of certain symptoms or drugs. Diagnostic schedules such as the FH-RDC may gradually educate informants about clinical terminology in the course of an interview.

In addition to the family tree, use of a structured interview based on specific diagnostic criteria is important for diagnostic accuracy. If the residents had requested more specific information about many relatives, the resulting diagnoses could have been more influential clinically than was the ambiguous information often recorded in the chart. For example, several relatives who were noted by the residents as being "hyper with mood swings" were actually diagnosed with alcoholism on the basis of research methods; only one relative with this chart description was research diagnosed with bipolar disorder, which the description might have implied. In a research setting, interviewing relatives with FH-RDC has been shown to significantly increase both accuracy and sensitivity in comparison with methods that use vaguely described criteria or none at all (8).

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Cardiac Rate and Rhythm in Panic Patients

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This study assessed cardiac rate and rhythm by ambulatory monitoring in 23 patients with panic disorder or agoraphobia with panic attacks. The patients had a higher than normal mean daily density of ventricular premature complexes (VPCs), but complex ventricular arrhythmias were uncommon. Heart rate was greater during panic intervals than during asymptomatic periods. The prevalence of arrhythmias within symptomatic intervals was similar during panic, partial panic, and anxiety and was significantly higher than during asymptomatic intervals. However, most panic episodes had no arrhythmias, and arrhythmias during panic intervals were simple VPCs.

(Am J Psychiatry 1987; 144:633–637)

Panic patients frequently report palpitations, racing heart, or a sensation of skipped beats both during and between panic episodes. Several studies have documented changes in cardiac rate but not rhythm during ambulatory monitoring of panic patients. These reports have shown normal 24-hour average heart rates (1) and rapid heart rate during most panic episodes (1, 2). In addition, unusual variability in heart rate has been observed in panic patients (paper by C.B. Taylor et al. presented at the 138th annual meeting of the American Psychiatric Association, Dallas, May 18–24, 1985).

Arrhythmias might also be expected in patients with panic attacks, since it has been suggested that there is a relationship between anxiety and cardiac arrhythmias in patients with neurocirculatory asthenia (3) and since a relationship has been found between psychological factors and ventricular arrhythmias in patients with symptomatic cardiac arrhythmias (4). However, although it has been suggested that changes in heart rate or rhythm may trigger panic episodes (5), the prevalence and character of cardiac rhythm disturbances in panic patients have not been well studied.

Documentation of cardiac rate changes and arrhythmias during panic episodes has both theoretical and clinical implications. Analysis of disturbances in rhythm and rate might provide clues to the pathogenetic mechanism of panic, and the study of cardiac rhythm during nonpanic periods might provide insight into underlying disorders of cardiovascular regulation in panic patients. Further, patients who develop rhythm disturbances during panic attacks might benefit from information about, or specific treatment of, these arrhythmias. The present study was therefore undertaken to document the frequency and complexity of cardiac rhythm disturbances during 24-hour ambulatory ECG monitoring in panic patients and to examine the prevalence and nature of arrhythmias during panic, anxiety, and nonanxious periods in these patients.

METHOD

The study sample consisted of 23 patients (11 men and 12 women) from the Payne Whitney Anxiety Disorders Clinic who met *DSM-III* criteria for panic disorder (N=6) or agoraphobia with panic attacks (N=17). Their mean age was 35 years (range=18–53 years). Diagnoses were confirmed by using the Structured Clinical Interview for DSM-III (6). Two patients had concurrent diagnoses of dysthymic disorder, and one had a past history of major depressive disorder. No other axis I diagnoses were made. The panic disorder illness was moderate to severe in all patients. No patient had a known cardiovascular illness, and all had had physical examinations with normal findings during the month preceding the study. All patients reported that they had been drug free for at least 2 weeks before the study, and no medications were prescribed at the time of the study.

Two-channel continuous ambulatory recordings made with modified V_1 and V_5 leads were obtained for all subjects. All of the recordings were initially scanned by a special technician who used simultaneous complex superimposition, cycle-length arrhythmiagraph, cycle-length sound frequency, and computer QRS complex and cycle-length evaluation for the identifica-

Presented in part at the 138th annual meeting of the American Psychiatric Association, Dallas, May 18–24, 1985. Received Aug. 23, 1985; revised Jan. 9 and Aug. 22, 1986; accepted Sept. 19, 1986. From the Departments of Psychiatry and Medicine, the New York Hospital-Cornell Medical Center, New York, N.Y. Address reprint requests to Dr. Shear, Anxiety Disorders Clinic, Payne Whitney Clinic, 525 East 68th St., New York, NY 10021.

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tion and quantification of disorders of impulse formation and conduction by means of an Avionics Trendsetter scanner. An experienced electrocardiographer reviewed the findings, with computer-assisted interactive quantification of all single ectopic complexes and identification of repetitive forms. Careful attention was given to excluding artifact from cumulative counts.

A mean of 23 hours of ambulatory recording per patient was examined (range=21–27 hours). Each ECG was analyzed for rhythm disturbance and mean and maximum heart rates. Analysis of supraventricular rhythm disturbance included quantification of the mean and peak numbers of atrial premature complexes (APCs) per 1,000 total beats over the entire recording period and tabulation of APC couplets, paroxysmal atrial tachycardia, atrial fibrillation, and atrial flutter when present. Analysis of ventricular rhythm disturbance included quantification of mean and peak ventricular premature complexes (VPCs) per 1,000 beats over the entire recording period.

In addition, VPCs were graded according to peak frequency and complexity by a system proposed by Lown and Wolf (7), which incorporates a hierarchical classification based on VPC frequency and the presence or absence of multiform VPCs, VPC couplets, ventricular tachycardia, and early-cycle beats. This system was originally developed to identify subjects at risk for sudden death, on the basis of early experience with patients in the coronary care unit setting, and has important theoretical limitations in nonischemic patients (8). However, no patient in the study had either early-cycle VPC forms (grade 5) or ventricular tachycardia (grade 4B), so the peak arrhythmia grade during the recording period represents a progression from no VPCs (grade 0) to infrequent simple VPCs (mean daily density <10/1,000 beats, grade 1) to frequent uniform VPCs (mean daily density >10/1,000 beats, grade 2) to multiform single VPCs (grade 3) to VPC couplets (grade 4A). The prevalence of ventricular ectopic beats generally increases with age (8) and has been associated with enhanced sympathetic activity.

ECG findings were related to symptoms experienced by patients during 15-minute intervals throughout the period of recording. All intervals during which a patient experienced a specific psychological symptom (e.g., panic attack or anxiety without panic) were examined for arrhythmias. Any rhythm disturbance found during a symptomatic interval was recorded on paper at standard speed and interpreted from hard copy by a cardiologist. Heart rate changes during panic episodes were assessed by comparing the most rapid heart rate found during that 15-minute interval with the most rapid rate for the previous 15-minute interval.

Patients were asked to record anxiety level, thoughts, and feelings during 15-minute intervals throughout the ambulatory ECG recording period and to record the time and type of symptoms that occurred during any panic episodes. All panic attacks met *DSM-III* criteria for panic episodes. Panic was described as sudden in onset and characterized by a feeling of extreme fear with associated somatic symptoms. All patients experienced chest pain or heart palpitations during panic, with variable combinations of other symptoms. Additional episodes classified as partial panic also occurred unexpectedly and included a sensation of sudden "rush" and fear of being out of control. However, partial panic episodes were characterized by fewer symptoms and less intensity than panic attacks and were usually described as aborted panic attacks. Most patients described anxiety as qualitatively different from panic. Anxiety was characterized by worry and tension that were focused on a dreaded or uncertain future event—for example, worry about a relative's health, a potential confrontation, a job problem, or hypochondriacal concerns or worry about having a panic attack.

In our statistical data, mean values are presented with the standard deviation as the index of dispersion. We assessed statistical significance by the unpaired or paired Student's t test, as appropriate, for the comparison of means and the chi-square test with Yates' continuity correction for comparison of proportions. We used nonparametric (Mann-Whitney) rank testing for comparison of means between groups of data with nonnormal distributions (mean and peak APCs and VPCs and peak Lown grade). Linear correlation was performed by the least squares method. Differences with $p \geq .05$ were not considered significant.

RESULTS

All patients experienced symptoms on the day of the recording. Five patients had full-blown panic attacks, 15 had episodes of partial panic, and 16 had nonpanic anxiety. Four patients had both anxiety and panic episodes, three had panic and partial panic, and 13 had both anxiety and partial panic. Panic attacks were present during 18 of the 15-minute intervals; there were 46 intervals containing partial panic and 175 intervals containing anxiety. Thirteen patients reported heart palpitations, none reported dyspnea, and two reported chest pain at some point during the monitored period. Most but not all of these symptoms occurred during the panic, partial panic, or anxiety periods.

For the group, the mean±SD daily heart rate was 79±12 beats/minute (mean minimum daily rate=51±8; mean maximum daily rate=131±17). The daily mean±SD APC density per 1,000 total beats was 2.0±5.7, and the daily mean±SD VPC density per 1,000 total beats was 2.6±7.8. There was a weak linear correlation between mean VPC density and mean daily heart rate ($r=.45$, $p<.05$) and a stronger correlation between mean VPC density and minimum daily heart rate ($r=.65$, $p<.001$). Mean VPC density was not correlated with age. Mean VPC density and

TABLE 1. Ventricular Premature Complex (VPC) Density and Complexity in 23 Patients With Panic Disorder Monitored for 24 Hours

Measure	Number of Subjects	
	Group 1 (N=5)[a]	Group 2 (N=18)[b]
Mean daily density per 1,000 beats		
0		9
0.001–0.01		4
0.01–0.1	2	2
0.1–1.0	2	1
>1.0	1	2
Peak Lown grade[c]		
0		9
1	2	7
2	1	
3	2	
4A		2

[a]Group 1=patients who reported at least one panic attack on the monitored day.
[b]Group 2=patients who reported no panic attacks on the monitored day.
[c]0=no VPCs, 1=infrequent simple VPCs (<10/1,000 beats), 2=frequent simple VPCs (>10/1,000 beats), 3=multiform single VPCs, 4A=VPC couplets.

APC density were linearly correlated with each other ($r=.64$, $p<.001$), as were mean VPC density and peak Lown grade ($r=.59$, $p<.01$).

None of the 23 patients had ventricular tachycardia or early-cycle VPC forms at any time during the ambulatory recording. Of the five patients who had panic attacks on the day of monitoring, all had VPCs during the period of ambulatory recording but not necessarily during the panic period. Two had infrequent simple VPCs (daily mean<10/1,000 beats), one had frequent simple VPCs (daily mean>10/1,000 beats), and two had multiform VPCs as their peak arrhythmia grade during the recording period; none had VPC couplets. Of the 18 patients who did not have panic attacks on the day of recording, nine had no VPCs, seven had only infrequent simple VPCs, none had multiform VPCs, and two had VPC couplets during the recording period.

There were no significant differences between the five patients who had panic attacks on the day of recording and the 18 patients who did not with respect to mean±SD age (41±6 and 33±9 years, respectively), distribution of the sexes, mean daily heart rate, minimum or maximum daily heart rate, and mean daily density of APCs. However, patients who had panic attacks during the day of ambulatory ECG recording had a higher daily mean±SD density of VPCs per 1,000 total beats (5.1±11.1 versus 1.9±6.9; $U=16$, $p<.05$, by Mann-Whitney rank testing) and a higher peak Lown grade during the period of recording (mean±SD=2.0±1.0 versus 0.8±1.2; $U=17$, $p<.05$, by rank testing) than patients who did not have panic attacks (see table 1). In contrast, there were no significant differences in mean daily heart rate variables, mean daily APC or VPC densities, or peak Lown grades between patients who did and patients who did not have partial panic attacks and between patients who did and patients who did not have episodes of anxiety on the day of recording.

The mean±SD peak heart rate during intervals of reported panic attacks in the five patients who had them was 108±14 beats/minute. In contrast, the mean±SD peak heart rate for the intervals immediately preceding the panic interval in these patients was 91±13 beats/minute ($t=2.79$, $df=1$, $p<.05$, by paired t test). The five patients who had panic attacks during the day of recording had panic symptoms during 18 of their 15-minute reporting intervals. Simple arrhythmias were observed in 28% (five of 18) of these intervals and occurred in 40% (two of five) of the patients who had panic attacks during one or more symptomatic periods. In each case, these arrhythmias were due to one or more simple (unpaired) VPCs. The 15 patients who reported partial panic attacks had a total of 46 intervals of partial panic. Arrhythmias were observed in 26% (12 of 46) of these intervals and occurred in 33% (five of 15) of the partial panic attack patients during one or more symptomatic periods. As with panic attacks, in each case these arrhythmias were due to simple VPCs. Thus, the only rhythm disturbances that occurred during symptomatic panic or partial panic periods were simple VPCs. No sustained arrhythmia or complex arrhythmia occurred during symptomatic intervals in these patients.

A greater variety of arrhythmias occurred during episodes of anxiety. The 16 patients who reported anxiety had a total of 175 anxiety intervals. Arrhythmias were observed in 37% (64 of 175) of these intervals and occurred in 69% (11 of 16) of the patients who experienced anxiety during one or more symptomatic periods. Arrhythmias observed were single APCs (27 instances in six patients), brief slow atrial tachycardia (three instances in three patients), nonsinus atrial rhythm (two instances in one patient), single VPCs (26 instances in five patients), and ventricular couplets (seven instances in one patient). In contrast, a sample of 54 randomly selected asymptomatic daytime, awake 15-minute intervals from the total patient sample revealed arrhythmias in only 4% (two of 54); $\chi^2=6.4$, $df=1$, $p<.025$, for the comparison with the prevalence of arrhythmia during panic attack intervals; $\chi^2=8.6$, $df=1$, $p<.005$, for the comparison with partial panic intervals; $\chi^2=20.2$, $df=1$, $p<.001$, for the comparison with anxiety intervals.

DISCUSSION

Cardiovascular symptoms are often prominent in patients' descriptions of panic attacks and are a central feature of current diagnostic criteria for panic disorder. However, the origin of these symptoms, which include chest pain, heart palpitations, shortness of breath, and syncopal feelings, is not clear. In particular, little is known of cardiac performance in panic patients either during or between panic episodes. Our observations represent a pilot study of a group of

patients with variable frequency of current panic attacks but all of whom had symptoms severe enough to motivate them to seek psychiatric treatment. There was a high rate of psychiatric morbidity on the day of ECG monitoring: 22% of the subjects experienced full-blown panic, 65% described partial panic, and 70% reported anxiety. This allowed us to compare daily rate and rhythm findings in patients who panicked with findings in those who did not and to compare cardiac rhythm during symptomatic and asymptomatic periods of the day. The study yielded a number of interesting findings.

First, although simple arrhythmias are common in clinically normal adults (8), the mean daily densities of APCs and VPCs in our patients, even though modest, were approximately twice as high as those previously reported in groups of subjects of similar age who did not have cardiovascular disease and in patients with mitral valve prolapse (9). However, it must be emphasized that clinically important ventricular arrhythmias were distinctly uncommon in these patients. Only two patients had VPC couplets and none had ventricular tachycardia during the period of ambulatory recording, and in neither patient were VPC couplets found during symptomatic panic or partial panic episodes. Most symptomatic periods were free of arrhythmias. All episodes of arrhythmia found in patients during periods of panic or partial panic were due to one or more simple VPCs. While single VPCs are generally not correlated with morbid events in nonischemic subjects (8), their occurrence as a "stress" response in otherwise normal people is well recognized. However, the timing of arrhythmias was strongly associated with intervals of reported panic, partial panic, and anxiety, since their prevalence during symptomatic periods (range=26%–37%) significantly exceeded that found during asymptomatic control intervals (4%) in the same patients. This may be partially explained by the direct relationship found in some subjects with frequent VPCs between increasing heart rate and increasing frequency of ventricular ectopy (10), possibly because of changes in autonomic tone. It is notable that there was no significant difference between panic and anxiety periods in the prevalence of arrhythmia. However, since most panic attacks were of relatively short duration (2–7 minutes), while generalized anxiety lasted for hours, the relative proportion of symptomatic panic time associated with rhythm disorders may have been higher than this analysis suggests.

A second interesting finding was the significantly higher overall mean daily frequency of VPCs in patients who panicked than in those who did not panic during the ambulatory recording. It is possible that this observation reflects changes in brain norepinephrine and cardiac sympathetic activity associated with expression of panic (11). Charney et al. (12) studied response to yohimbine in patients with agoraphobia and panic disorder and found that patients with a high frequency of panic attacks had a greater 3-methoxy-4-hydroxyphenylglycol (MHPG) response, a larger increase in blood pressure, more somatic symptoms, and higher self-rated anxiety than those with a low frequency of panic. Moreover, patients can often identify panic days or "bad days" shortly after awakening in the morning. Liebowitz et al. (13) reported differences in baseline measures between panic disorder patients who experienced a panic attack after sodium lactate infusions and those who did not, and we have noted a trend toward a higher average 24-hour blood pressure on panic days than on nonpanic days (unpublished manuscript). These findings support the hypothesis that increased central sympathetic activity is related to the development of panic.

We documented a mean heart rate elevation and a high prevalence of generally simple arrhythmias during anxiety and panic episodes. The mechanism for production of these changes is likely to be related to centrally mediated autonomic regulation, since the patients we studied were free of underlying heart disease and showed normal heart rate and rhythm stability during asymptomatic periods in a naturalistic environment. Further work is necessary to determine whether the cardiac findings are specific to patients with panic disorder or related to a nonspecific increase in arousal or stress. Panic patients often hyperventilate, and it is possible that our findings were manifestations of metabolic changes secondary to hyperventilation. Studies are underway to determine the frequency of arrhythmia in other psychiatric populations and normal subjects during stressful activities and hyperventilation. Some reports have suggested that patients with anxiety disorders may have higher cardiovascular mortality (14), and several studies have documented untoward effects of anxiety in patients or animals who have organic heart disease.

On the other hand, our patients had normal 24-hour average heart rates and a low prevalence of arrhythmias during asymptomatic periods. These findings are consistent with results of Freedman et al. (1), which suggested that underlying cardiovascular function is normal in these patients. Other findings that support the presence of normal underlying cardiovascular function in patients with panic disorder include reports by Grunhaus et al. (15) showing normal blood pressure and prolactin response to cold pressor testing and by Moreau et al. (16) showing normal heart rate and blood pressure response to auditory tones and to mental arithmetic. Further, we (17) have demonstrated normal heart rate and blood pressure responses to positional change and the Valsalva maneuver as well as normal 24-hour blood pressure in panic disorder patients.

In summary, this study documents the presence of generally simple cardiac arrhythmias in panic disorder patients and also demonstrates a higher prevalence of these rhythm disturbances during symptomatic periods. These findings support the concept of panic disorder as an autonomic nervous disturbance. However, it is apparent that changes in rate and rhythm during both panic and anxiety episodes are rather

modest. This is consistent with the observation that cardiovascular morbidity is not strongly associated with the diagnosis of panic disorder. Further work is necessary to clarify the relationship between psychological and cardiovascular symptoms in these patients.

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Dream Process in Asthmatic Subjects With Nocturnal Attacks

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Polygraphic sleep recordings were made and dream reports collected over 3 consecutive nights for 12 asthmatic subjects with nocturnal attacks and 12 matched normal control subjects. The asthmatic group 1) had more episodes of a vivid impression of dreaming without recollection of dream content ("white dreams") after awakening spontaneously in the morning (nights 1 and 2) and after awakening immediately following REM sleep (night 3), 2) used shorter sentences in dream narrations, and 3) had no dream recall when awakened during nocturnal asthma attacks. The authors suggest that conflictual material emerging during REM or other sleep stages may contribute to the occurrence of nocturnal attacks but is repressed on awakening.

(Am J Psychiatry 1987; 144:638–640)

Asthma has marked diurnal variations. Patients commonly display symptoms that arise largely during sleep, and even when symptoms occur throughout the day they are usually worse at night. In two previous studies (1, 2), only 15 of 315 nocturnal asthma attacks occurred in the first 2 hours of the night; most of them occurred toward the end of the night, when REM sleep is more abundant. Death from asthma also occurs more commonly during the night and in the early morning.

It is a common clinical observation that patients afflicted with psychosomatic illnesses, including asthma, report fewer dreams during psychotherapy (3) than do normal subjects, and their dreams are described as lacking fantasy or visual imagery. Our clinical experience confirms this assertion. During psychotherapy asthmatic subjects reported frequent nightmares (like "being strangled" or "being drowned") associated with nocturnal attacks (4–6). However, to our knowledge these clinical impressions have never been confirmed by direct observations of patients during nocturnal attacks. The aim of the present study was to answer the following questions.

1) Do asthmatic subjects report less dream content on spontaneous awakening than matched normal subjects?

2) Do they recall less dream content when awakened after REM sleep in the laboratory?

3) Are nocturnal asthma attacks accompanied by dream recall?

4) Are physiological correlates of the dreaming process, such as REM density, different in asthmatic subjects?

5) Is their dream content different from that of control subjects?

6) Do asthmatic subjects with particular personality traits, namely alexithymia, differ from control subjects in terms of dream recall?

METHOD

We studied 12 subjects (four men and eight women) who satisfied the criteria for asthma of the American Thoracic Society (7). These patients were in a clinically unstable state; they reported severe diurnal symptoms (such as shortness of breath, coughing, and wheezing) and nocturnal awakening due to asthma. Control subjects were matched for sex and age (±2 years). They were in good health and had no history of respiratory disease or any other psychosomatic illness. At the time of the study none of the asthmatic subjects or the matched control subjects was receiving psychotropic medications or hypnotics. Two asthmatic subjects used bronchodilators regularly (salbutamol inhaler with inhaled beclomethasone), and six used them occasionally; the others took no medication. Before entering the study, eight asthmatic subjects underwent a psychological evaluation that included a structured interview (8) conducted by two psychiatrists with special expertise in psychosomatic medicine. (Four patients refused to have the interview.) Each of the eight subjects was then rated independently by the two interviewers on the Schalling-Sifneos Scale (9) for degree of alexithymia. The range of the scale is 0–10; a score of 6 or above was considered of clinical

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Supported by the CAFIR Foundation, Université de Montréal, and the Association Pulmonaire du Québec.

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significance. The scale is not fully validated; consequently, any correlation between the scale scores and the sleep or dream variables should be interpreted with caution.

Polygraphic recordings of sleep and respiration were performed during 3 consecutive nights in the sleep laboratory. Sleep stages were scored by the standard method (10). During the first 2 nights sleep structure was studied; nocturnal symptoms were documented; spirometry was done before the asthmatic subjects went to sleep, when they awoke with asthma symptoms, and when they awoke in the morning; and dream reports were collected when the subjects spontaneously awoke in the morning. The third night was concerned with subjects' dream reports after they were awakened following each REM period that lasted 5 minutes or more. The technician, who was instructed to wait for the end of the REM period (1 minute of non-REM sleep) before entering the room, asked standard questions about dream recall and content. No attempt was made to have the subject associate on the dream content, since this might have interfered with the normal progression of sleep. Subjects were simply asked whether or not they were dreaming before being awakened and, if so, to report any element of the dream content. The technician recorded the dream narration for further analysis and then suggested that the subject return to sleep.

There is some evidence that REM density (i.e., the number of REMs per minute) is positively correlated with the dramatic intensity and visual imagery of the dream content. Consequently, REM density was calculated during 1 night for eight asthmatic subjects and their matched control subjects. REM density was defined in this study as the percentage of 2-second periods of sleep in which REMs were detected. Results reported in the present paper were collected during a larger study of nocturnal asthma attacks and nocturnal changes in respiratory function and sleep organization. Further methodological information has been published elsewhere (11–13). Statistical analysis was performed, using unpaired t tests for proportions, and the level of statistical significance was set at less than .05.

RESULTS

After spontaneously awakening in the morning following nights 1 and 2, a total of 10 asthmatic and 10 control subjects reported that they had dreamed during the previous night. However, only two asthmatic subjects could recall some element of the dream content, compared to eight control subjects ($t=3.35$, $df=18$, $p<.01$).

Asthmatic subjects reported more dreaming experience than control subjects, although not significantly so, on awakening after REM sleep on night 3. The numbers of awakenings for the asthmatic and control groups were 43 and 46, respectively, but asthmatic subjects reported 35 (81%) dreaming experiences versus 28 (61%) for control subjects. Moreover, more asthmatic than control subjects had the vivid impression of "coming out from a dream" without the ability to remember any element of the dream content (nine versus two subjects; $t=2.09$, $df=61$, $p<.05$). We suggest the term "white dream" for this phenomenon of a vivid sensation of dreaming without any content. It occurred repeatedly in five asthmatic subjects, three of whom were the most alexithymic ones on the basis of the Schalling-Sifneos scale and the psychological evaluation.

Eight asthmatic subjects experienced 26 nocturnal attacks during the study. Although attacks were more numerous at the end of the night, when REM sleep was more abundant, they were not proportionally more frequent in REM sleep, and four attacks occurred before the first REM sleep period. These results have been published in detail elsewhere (11–13). None of the asthmatic subjects reported that he or she was dreaming when aroused at the time of a nocturnal attack, even when the attack occurred during REM sleep ($N=5$).

The duration of each sleep stage was not significantly different for the 3 nights of recording for control subjects and asthmatic subjects. REM latency, REM efficiency, and total duration of REM sleep were also similar. These results and data on breathing patterns have been reported in detail elsewhere (11). REM density was slightly higher in asthmatic subjects (mean±SD=15.5%±4.3%) than in normal subjects (12.1%±3.9%), but the difference was not statistically significant.

The two groups did not display major differences in the semantic aspect of dream narration except for more references to body sensations (such as "My heart was jumping" or "I had no pain") by asthmatic subjects. However, in analyzing the syntactic aspects of 21 dream reports for the asthmatic subjects and 19 for the control subjects (nights 1–3), we found that the asthmatic subjects used shorter sentences (11.1±6.5 words versus 18.9±9.4 words; $t=6.19$, $df=194$, $p<.0001$) and fewer sentences (4.2±2.0 versus 5.7±2.5; $t=2.10$, $df=38$, $p<.05$). One asthmatic subject elaborated much more than any other subject, using 150 and 200 words, respectively, for two dreams; nevertheless, her sentences were as brief as those of the others (mean=7.8 words). This subject was not included in the statistical analysis.

Alexithymia is defined as the lack of emotive perception and expression (9). Considered an emotive problem or an adaptive process, it is commonly found in psychosomatic patients. This concept has been described extensively in the psychosomatic literature (3, 9, 14). Four asthmatic subjects with a high degree of alexithymia (Schalling-Sifneos scale score of 6–10) reported white dreams in seven of eight awakenings during nights 1 and 2 and in six of nine REM interruptions during night 3. This small set of data did not allow any valuable statistical analysis.

DISCUSSION

In our study, asthmatic subjects in an unstable clinical state dreamed at least as often as control subjects, since they reported even more dreams when awakened following REM sleep in the laboratory. Biological indices of the dreaming process also led to this conclusion: REM density, which is probably the best indicator of the dreaming process, was normal in asthmatic subjects.

However, asthmatic subjects had poor dream recall on spontaneous awakening in the morning and when aroused from REM sleep. One can speculate about the mechanism responsible for the lack of recall. Some aspects of the protocol, such as waiting for 1 minute of non-REM sleep before arousing the subject, may have resulted in a lower percentage of dream recall, but this factor cannot explain the difference between the two groups. One may question whether the nocturnal hypoxemia recorded in the asthmatic subjects might be the cause of the poor dream recall. Mild oxygen desaturations were seen at times in asthmatic subjects but could hardly explain the poor dream recall (12), since white dreams were reported repeatedly by subjects who did not show significant (>4%) oxygen desaturation. Psychological mechanisms such as repression of conflictual material are more likely to be involved. This interpretation is consistent with observations made during psychotherapy (4, 5, 15) in which dream content is retrieved that is closely related to death anxiety (for example, when it involves being strangled or drowned).

It should be pointed out that a subgroup of nonpsychosomatic patients was also shown to have difficulty remembering dreams (16). This observation may lead to questions about the specificity of results obtained in asthmatic subjects. This question is very important and will require further research comparing different patient populations.

It was surprising that subjects awakened at the time of nocturnal asthma attacks during REM sleep had no dream recall. A possible interpretation would be an absence of correlation between dreams and nocturnal attacks. A more likely explanation would be that dreams leading to nocturnal attacks (as sometimes reported by patients during psychotherapy) are strongly repressed (17). An alternative but complementary explanation would be that physiological distress at the time of nocturnal attacks makes the patient less attentive to the dream process. The lack of dream recall may resemble some of the amnesia occurring after major traumatic experiences. Furthermore, alexithymia has also been described in patients who have suffered traumatic shock (3). This phenomenon can be viewed as a defensive process against negative effects associated with threatening thoughts or images recurring in dreams.

In 1977 Hoppe (18) pointed out the similarity in operational thinking between psychosomatic and commissurotomy patients, and he raised the hypothesis of a "functional commissurotomy" in cases of severe psychosomatic disturbances. Dream studies further support this hypothesis. As psychosomatic subjects, commissurotomy patients show an impoverishment of dreams (18). Furthermore, as in asthmatic patients, a high frequency of white dreams was recently found in one epileptic subject after posterior section of the corpus callosum, the main cerebral commissure in man (19).

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CSF Corticotropin-Releasing Hormone in Depressed Patients and Normal Control Subjects

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The authors studied CSF corticotropin-releasing hormone (CRH) and plasma cortisol in 22 depressed patients and 18 normal control subjects. CRH levels were similar in the two groups. Depressed patients who were nonsuppressors on the dexamethasone suppression test had significantly higher levels of CRH than suppressors did. The depressed patients' CRH levels were significantly correlated with 4:00 p.m. postdexamethasone plasma cortisol levels. While the inclusion of a depressed patient with an outlier CRH value resulted in the loss of statistical significance for both of these findings, the authors suggest that these results support the hypothesis that hypercortisolism in depressed patients in part reflects a defect at or above the hypothalamus, resulting in hypersecretion of CRH.

(Am J Psychiatry 1987; 144:641–645)

Hypercortisolism is one of the best documented biological abnormalities in depression; it occurs in 40%–60% of depressed patients (1). Although the etiology of this hypercortisolism has not been definitively elucidated, Gold et al. (2) recently reported that hypercortisolemic depressed patients showed blunted ACTH responses to endogenous corticotropin-releasing hormone (CRH), indicating that the pituitary corticotroph cell was appropriately restrained by high levels of circulating cortisol. Moreover, these authors noted that a continuous infusion of CRH in normal volunteer subjects reproduced the pattern and magnitude of hypercortisolism typically seen in depressed patients (3). On the basis of these data, it was hypothesized that hypersecretion of cortisol in depression reflects a defect at or above the hypothalamus that results in the hypersecretion of CRH. In support of this hypothesis was a study by Nemeroff et al. (4) that showed increased levels of CSF CRH in depressed patients.

To further explore the hypothesis that endogenous CRH is involved in the hypothalamic-pituitary-adrenal (HPA) abnormality found in depression, we report here a study that compared the CSF CRH levels of depressed patients and normal control subjects. We also correlated CSF CRH levels with the response of plasma cortisol to the administration of dexamethasone. We reasoned that depressed patients who showed the most resistance to the glucocorticoid suppressive effect of dexamethasone might manifest the highest levels of CRH in the CSF.

METHOD

Twenty-two depressed inpatients (three male and 19 female) participated in the study and were compared with 18 normal control subjects (11 male and seven female). All participants gave informed consent. The mean±SD age of the patients was 40.9±10.4 years and of the control subjects, 31.1±8.4 years. The patients were given diagnoses on the basis of clinical interviews by two psychiatrists (A.R. and D.P.) using *DSM-III* criteria; they reached agreement in consensus discussions about each case. Fifteen patients received the diagnosis of major depressive episode with melancholia, and seven received the diagnosis of major depressive episode without melancholia. Of the group of depressed patients, 15 had unipolar and seven had bipolar depression. Two of the patients with the bipolar type showed psychotic features. The mean±SD number of previous affective episodes was 3.3±3.2 (one depressed patient, not included in this mean, had had 40 episodes). The mean±SD duration of the present depressive episodes was 7.6±6.7 months. None of the patients had an ongoing axis II diagnosis. The Hamilton Rating Scale for Depression (5) was completed for each patient; the mean±SD score was 26.9±7.1. The 18 normal control subjects were interviewed by a psychiatrist to rule out past or current psychiatric disorder and to ascertain that they were also without any family history of psychiatric disorder. All of the control subjects were physically healthy and had normal results on a physical examination, chest

Received Aug. 30, 1985; revised Feb. 25, July 23, and Oct. 3, 1986; accepted Nov. 3, 1986. From the Clinical Neuroscience Branch and the Biological Psychiatry Branch, NIMH, Bethesda, Md.; and the Developmental Endocrinology Branch, National Institute of Child Health and Human Development, Bethesda, Md. Address reprint requests to Dr. Roy, Laboratory of Clinical Studies, National Institute on Alcohol Abuse and Alcoholism, Bldg. 10, Rm. 3B-19, 9000 Rockville Pike, Bethesda, MD 20892.

X-ray, ECG, and routine blood tests; they were studied as inpatients.

Patients and control subjects followed a low-monoamine, alcohol-free, and caffeine-restricted diet for at least 2 weeks before the study. Those patients who were taking psychotropic medications were slowly withdrawn from medication and were medication free for at least 2½ weeks before their lumbar puncture. The mean±SD time free of medication was 9.1±18.2 weeks (one patient, not included in this mean, had not received psychotropic medication for 12 years). Lumbar punctures were performed between 8:30 a.m. and 9:00 a.m., with the subjects in the lateral decubitus position. All subjects had fasted and rested in bed since midnight before the lumbar puncture. The first 10 ml of CSF were collected as a pool and placed on ice at the bedside, subsequently aliquoted, and then frozen at −80°C until the time of assay. The same aliquot was used to measure CRH for all depressed patients and control subjects.

CSF CRH was measured in extracted CSF by radioimmunoassay, as previously described (6), with the following modifications. A more sensitive antibody (TS-3) was used, with an equilibrium constant of 2.3×10^{10} liters/mol. Sensitivity of 1.5–2.0 pg per tube with a median effective dose of 21.0 pg per tube was achieved by using a disequilibrium technique of delayed tracer addition. There were no significant cross-reactivities (<0.01%) between the TS-3 antisera and growth-hormone-releasing hormone, luteinizing-hormone-releasing hormone, oxytocin, arginine vasopressin, ACTH (amino acids 1–39), β-endorphin, thyrotropin-releasing hormone, human luteinizing hormone, human follicle-stimulating hormone, human chorionic gonadotropin, human growth hormone, human prolactin, porcine insulin, angiotensin I, porcine vasoactive intestinal peptide, substance P, somatostatin, neurotensin, leu-enkephalin, or met-enkephalin.

The CSF was extracted by means of disposable reverse-phase extraction minicolumns. Silica cartridges (Sep-Pak C18, Waters Associates, Inc., Milford, Mass.) were washed with 10 ml of methanol followed by 15 ml of triethylamine formic acid (TEAF) buffer (10.73 ml of formic acid per liter of H_2O); pH was brought to 3.2 with triethylamine. One milliliter of human CSF was applied to the prepared cartridge through a 3-ml disposable syringe at a flow rate of 1 ml/minute. This flow was achieved by using gravity and capillary action. The 3-ml syringe was washed with 1 ml of TEAF buffer at the same flow rate. Another syringe loaded with 10 ml of TEAF buffer was applied to the cartridge, and the solution was pushed through at 5 ml/minute. The washed sample was eluted from the cartridge with 6 ml of a solution of 20% TEAF buffer and 80% acetonitrile and collected into a polystyrene tube. The eluate was dried by vacuum evaporation in a Savant Speed Vac (Savant Instruments, Inc., Hicksville, N.Y.). Dried samples were reconstituted by using radioimmunoassay buffer and were allowed to sit without mixing for 16–24 hours at 4°C; at the end of this period, the extracts were vortexed. Sensitivity was improved by extracting 1 ml of sample and reconstituting it with 0.5 ml of assay buffer for a twofold concentration. This extraction procedure routinely gives better than 85% recovery (based on recovery of known amounts of exogenous CRH added to CSF). We examined parallelism by using a CSF pool that had measurable levels of human CRH (mean±SD=31.0±2.5 pg/ml). These two CSF pools were used as controls. Known quantities of human CRH were added to these pools to obtain concentrations higher than those of the control subjects. The intra-assay and interassay coefficients of variation for the CRH radioimmunoassay were 6% and 12%, respectively.

Two days after the lumbar puncture, the dexamethasone suppression test (DST) was given to all the depressed patients and all but one control subject, according to the method of Carroll et al. (7). Blood for cortisol determinations was drawn at 4:00 p.m. and 11:00 p.m. on the following day. (Blood was not drawn from the control subjects at 11:00 p.m. on the day after administration of dexamethasone.) Cortisol determinations were made by radioimmunoassay. A maximum postdexamethasone cortisol value of 5 μg/dl or more identified dexamethasone nonsuppressors. The sensitivity of the plasma cortisol assay was 0.2–0.7 μg/dl. The radioimmunoassay we used was specific for cortisol; its cross-reactivity was 100% for cortisol, 2.5% for corticosterone, and less than 0.02% for other steroids. The intra-assay and interassay coefficients of variation were 5% and 11%, respectively.

In the statistical analysis, Student's t test and Pearson's method of correlation were used. One depressed patient had a CSF CRH value more than 3 SDs greater than the mean and is hereafter referred to as the "outlier." A second assay showed a similar CSF CRH value for this patient, who also had very high levels of other biological variables. Thus, all of the data were analyzed both excluding and including the data of this patient.

RESULTS

There was no significant difference between the total group of depressed patients and the control subjects in CSF CRH levels, when the depressed outlier was either excluded (mean±SD=39.49±15.33 and 37.21±10.38 pg/ml, respectively; t=0.53, df=37) or included (mean±SD=45.10±30.29 and 37.21±10.38 pg/ml, respectively; t=1.05, df=38) (see figure 1).

Although there was no significant difference in CSF CRH levels between depressed and control groups, depressed patients who were DST nonsuppressors (N=11) had significantly higher CSF CRH levels than DST suppressors (N=10) (mean±SD=45.73±18.36 and 32.63±6.95 pg/ml, respectively; t=2.1, df=19, p<.05). However, when the depressed outlier, a DST suppressor, was included, there was no significant

FIGURE 1. CSF CRH Levels of 22 Depressed Patients and 18 Normal Control Subjects

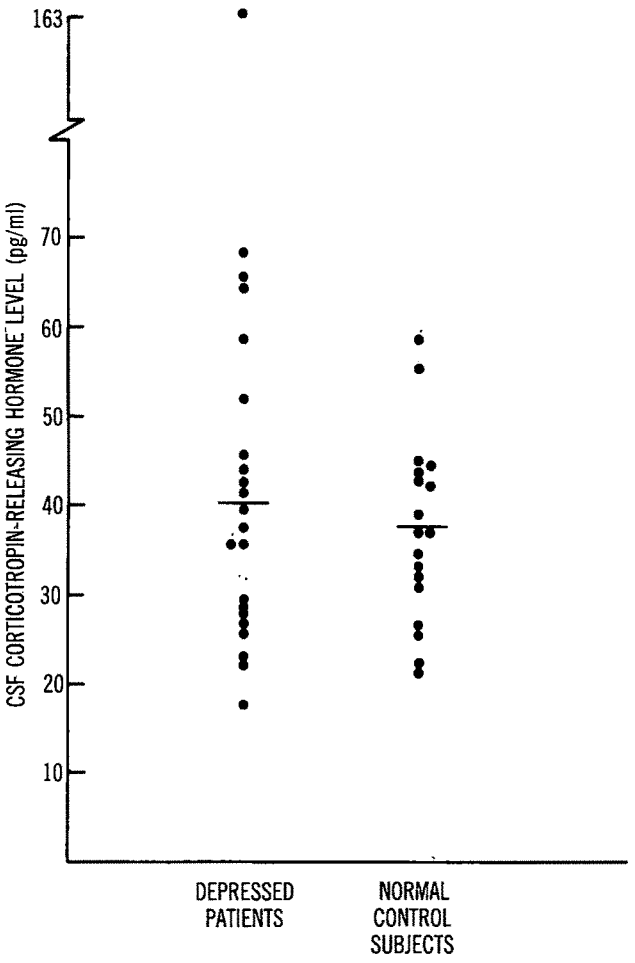
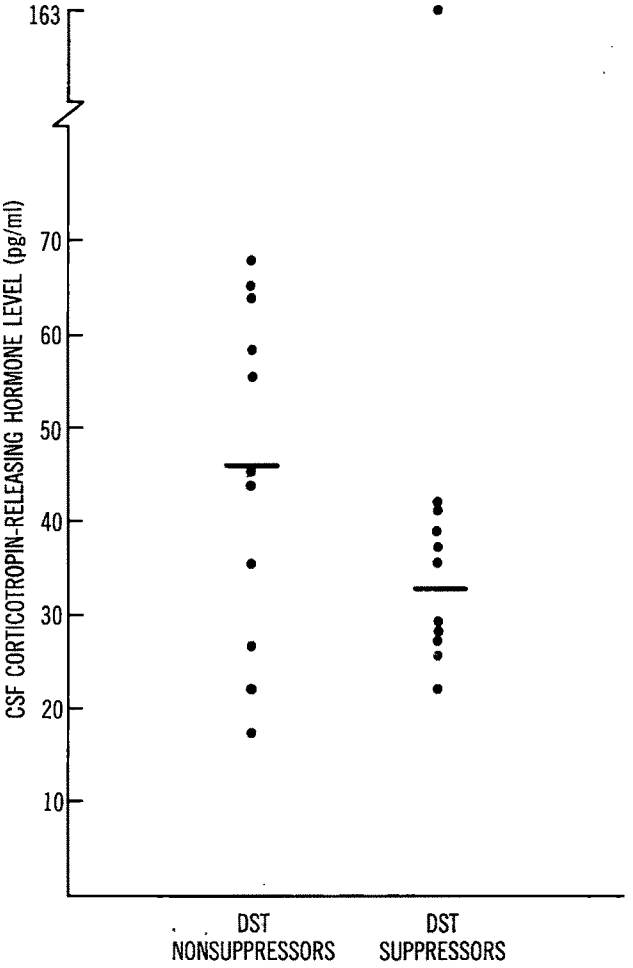


FIGURE 2. CSF CRH Levels of 11 Depressed DST Nonsuppressors and 11 Depressed DST Suppressors



difference (mean±SD=45.70±18.36 and 44.48±39.95 pg/ml, respectively; t=0.09, df=20) (see figure 2). Also, it should be noted that CSF CRH levels among the DST nonsuppressors were not significantly higher than among the control subjects (mean±SD=45.73±18.36 and 37.21±10.38 pg/ml, respectively; t=1.6, df=27).

Among the depressed patients (excluding the unipolar outlier), we found significant correlations between levels of CSF CRH and 4:00 p.m. postdexamethasone plasma cortisol levels in the total group (N=21, r=.66, p<.001) (see figure 3) and in the unipolar group (N=14, r=.66, p<.01). However, the inclusion of the outlier resulted in the loss of these significant correlations in both the total group (N=22, r=.19, n.s.) and the unipolar group (N=15, r=.08, n.s.). There was also a trend for a significant correlation between CSF CRH and 4:00 p.m. postdexamethasone plasma cortisol levels in the patients who were DST nonsuppressors (N=11, r=.56, p<.10). This correlation was unaffected by the outlier, who was a DST suppressor.

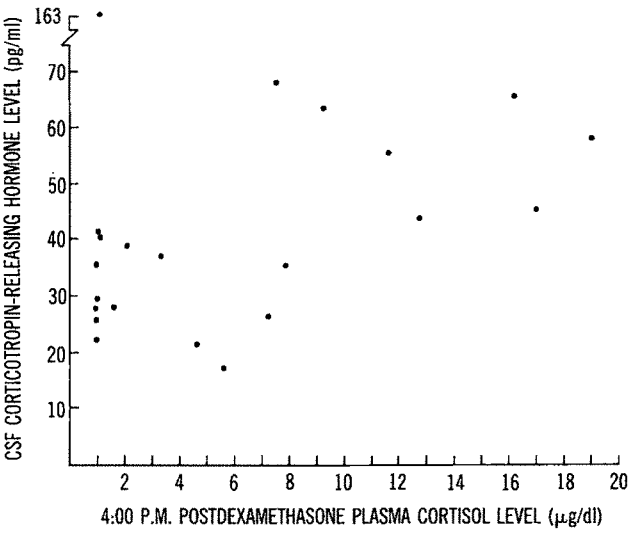
Among the control subjects (N=17) there were no significant correlations between CSF CRH and plasma cortisol levels either at 4:00 p.m. before dexamethasone (r=−.01) or at 4:00 p.m. after dexamethasone (r=.21). Among the depressed patients there were no significant correlations between CSF CRH and plasma cortisol levels either at 4:00 p.m. before dexamethasone (N=20, r=.35) or at 11:00 p.m. after dexamethasone (N=19, r=.33).

There were no significant correlations between CSF CRH levels and age in either the depressed patients (r=.12) or the control subjects (r=−.33). Among the depressed patients, excluding the outlier, there were no significant correlations between CSF CRH levels and Hamilton depression scale scores (N=21, r=.04).

DISCUSSION

We found no significant difference in CSF CRH levels between the total group of depressed patients and the control subjects. The depressed patients who were nonsuppressors on the DST showed significantly higher CSF CRH levels than depressed patients who

FIGURE 3. CSF CRH Levels and Postdexamethasone Plasma Cortisol Levels of 22 Depressed Patients



were DST suppressors, and the depressed patients showed significant correlations between CSF CRH levels and postdexamethasone plasma cortisol levels at 4:00 p.m. However, it should be noted, first, that inclusion of a depressed patient with an outlier CSF CRH value led to the loss of these significant findings and, second, that the DST nonsuppressors did not have CSF CRH values significantly greater than those of the control subjects. Nonetheless, we tentatively suggest that these results support the hypothesis that the hypercortisolism and cortisol escape from dexamethasone administration found among depressed patients may partly reflect a defect at or above the hypothalamus that results in hypersecretion of CRH (8).

Our finding that CSF CRH levels were similar in the total group of depressed patients and in the control subjects has also been reported by Davis et al. (9) and is in apparent conflict with the results of the study by Nemeroff et al. (4), which showed increased CSF CRH levels in depression. The discrepancy with the results of Nemeroff et al. may be related to the fact that their patients were first-episode, treatment-responsive patients, whereas our patients had recurrent affective disorder. However, our finding that the DST nonsuppressor subgroup of depressed patients had significantly higher levels of CSF CRH than the DST suppressors (when the outlier was excluded) is compatible with the findings of a study (10) showing that CSF CRH levels of hypercortisolemic, underweight patients with anorexia nervosa were significantly higher than those of normal control subjects but subsequently fell to normal when the patients were refed and the hypercortisolism resolved. (In that study there was also a positive correlation between depression ratings and CSF CRH levels in the weight-corrected patients with anorexia nervosa.)

The correlations between postdexamethasone plasma cortisol levels and CSF CRH levels in our group of depressed patients are in contrast to the data of Davis et al. (9) and Nemeroff et al. (4), who found no such correlations. We cannot fully account for the discrepancy in these studies. However, it should be noted that including the data of the DST-suppressor outlier resulted in the loss of the significant correlation in our study, although the trend for a significant correlation remained among the patients who were DST nonsuppressors. Also, discrepancies between studies could reflect differences in patient population, storage time of CSF samples, or assay methodology. Another possible source of these differences is the temporal relationship between lumbar puncture and administration of the DST. For all of the depressed patients and control subjects in this study, the 11:00 p.m. dose of dexamethasone was administered 36 hours after the lumbar puncture.

The source of CRH in the CSF has not been definitely elucidated. CRH cell bodies and terminal fields are located not only in the hypothalamus but also in the cortex, limbic system, and brainstem (11–13). Presumably, any of these could contribute to the CSF content of CRH. The function of CRH in the CSF is equally uncertain. However, studies in experimental animals show that intracerebroventricular administration of CRH produces activation of the HPA axis (14) as well as a variety of other physiological and behavioral responses characteristic of the response to stress (and depression) (15–17).

Although this study tentatively suggests a role for CSF CRH in the hypercortisolism found in depressed patients, it should be noted that the regulation of the HPA axis is complex and only incompletely understood (18). Thus, CRH is probably not the only factor involved in the hypercortisolism of depression. Other central nervous system peptides such as vasopressin (19) have also been recognized as influencing the pituitary corticotroph cell in both in vivo and in vitro studies (18). In vitro studies show that a variety of other factors can influence the pituitary corticotroph cell, including catecholamines and vasoactive intestinal peptide (18).

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Influence of Age and Relative Weight on Cortisol Suppression in Normal Subjects

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Richard C. Mohs, Ph.D., and Kenneth L. Davis, M.D.

The authors examined the effects of certain nonpsychiatric variables on dexamethasone suppression test (DST) results. Sixty physically healthy, nondepressed, nondemented adults participated in a standard outpatient 1-mg DST. Postdexamethasone plasma cortisol concentrations were higher in older subjects and were lower in more obese subjects. The authors conclude that age and relative weight influence cortisol suppression in healthy subjects.

(Am J Psychiatry 1987; 144:646–649)

The dexamethasone suppression test (DST), as used in psychiatric diagnosis, is generally considered positive when certain arbitrary levels of postdexamethasone serum cortisol are exceeded (1). There is evidence that age, plasma cortisol levels, and recent weight loss may significantly influence the results of the DST (2–9).

The present study systematically investigated the suppressibility of cortisol in psychiatrically and medically normal adults of different ages, from youth to old age. In addition to age and cortisol levels, factors considered were the subjects' degree of obesity, consumption of stimulant beverages, and smoking.

METHOD

Healthy volunteers were recruited through newspaper advertisements and senior citizen groups. Exclusion criteria included acute or chronic illness, regular use of medications (including topical steroid preparations), and a history of depression or memory problems. Screened volunteers were seen at the Bronx Veterans Administration (VA) Medical Center or the Mount Sinai Clinical Research Center. Informed consent was obtained from all subjects after the procedures had been fully explained. A complete medical and psychiatric history (including a standard question about recent weight loss) was obtained for each patient, and physical examination, neurological examination, mental status evaluation, Mini-Mental State test (10), ECG, and urinalysis were performed. Blood was drawn for thyroid function studies, VDRL, SMA-18, and baseline (9:00 a.m.) plasma cortisol concentration. Each candidate was examined directly by a senior psychiatrist (M.F.W.), who paid special attention to any history of depression and signs and symptoms suggestive of depression or dementia.

Of the 77 subjects initially examined, data from 15 were excluded for medical reasons. Two subjects did not return for postdexamethasone testing, so that the final number of qualified subjects was 60. We obtained data at all four points for only 55 of these subjects. Nondisqualifying conditions among the subjects included untreated moderate hypertension, hydrochlorothiazide use, alcoholism with several years of abstinence, and asymptomatic ECG abnormalities. All 60 of the subjects had Mini-Mental State scores of 24 or more (maximum possible score is 30). Their mean±SD age was 50.9±19.1 years (range=19–88 years); 16 subjects were 65 years old or older, and only two were over 80 years of age. There were 35 men and 25 women.

Subjects reported for their medical workup in a fasting state. After completing the medical workup they were given 1 mg of dexamethasone (two 0.5-mg tablets of dexamethasone, Barr Laboratories) to take home. They were told to take the tablets at 11:00 p.m. on a specified night and to return the day after so that blood could be drawn at 8:00 a.m., 12:00 noon, and 4:00 p.m. Compliance was excellent; all subjects had measurable plasma dexamethasone concentrations at 8:00 a.m. after dexamethasone ingestion. They were asked to refrain from drinking coffee or tea and from smoking cigarettes for an hour before all blood samplings but were not asked to fast for postdexamethasone blood drawings. No attempt was made to monitor or control their level of physical activity. One

Presented at the annual meeting of the American Gerontological Society, New Orleans, Nov. 22–26, 1985. Received Feb. 3, 1986; revised Aug. 15 and Nov. 17, 1986; accepted Dec. 24, 1986. From the Department of Geriatrics, Mount Sinai Medical Center; and the Department of Psychiatry, Bronx Veterans Administration Medical Center, New York, N.Y. Address reprint requests to Dr. Weiner, Department of Psychiatry, Southwestern Medical School, 5323 Harry Hines Blvd., Dallas, TX 75235.

Supported by a grant from the John A. Hartford Foundation.

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TABLE 1. Cortisol Values in Normal Volunteer Subjects in Different Age Groups After Administration of 1 mg of Dexamethasone

		8:00 a.m. (N=50)			12:00 noon (N=56)			4:00 p.m. (N=55)		
		Cortisol (μg/dl)			Cortisol (μg/dl)			Cortisol (μg/dl)		
Age (years)	N	Mean	SD	Nonsuppressors	Mean	SD	Nonsuppressors	Mean	SD	Nonsuppressors
20–29	7	1.0	0.9	0	0.8	0.5	0	1.3	1.6	0
30–39	9	1.5	0.5	0	1.3	0.5	0	1.4	0.7	0
40–49	6	1.0	0.4	0	0.9	0.4	0	1.7	1.2	0
50–59	11	1.3	0.7	0	1.2	0.6	0	1.9	2.5	1
60–69	11	1.6	0.5	0	1.4	0.6	0	2.0	1.0	0
70–79	10	1.9	0.9	0	1.9	1.4	1	2.0	1.5	1
80–89	2	1.4	0.5	0	5.6	6.8	1	4.8	5.9	1

woman, on her way to the hospital, became nauseated and overheated on a crowded bus; she got off, vomited, and then walked 15 blocks to her appointment. Her 4:00 p.m. postdexamethasone plasma cortisol level (32.2 μg/dl) was excluded from statistical analysis.

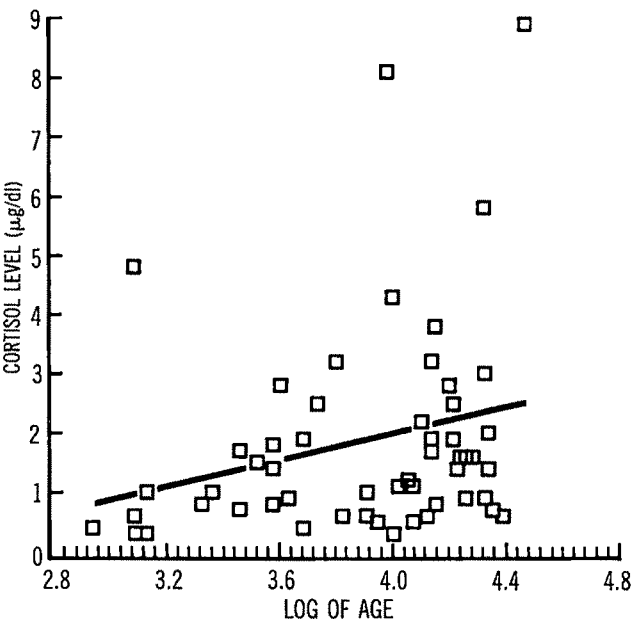
Blood for plasma cortisol determination was collected in heparinized tubes that were immediately centrifuged for 15 minutes at −4°C. Plasma was frozen at −20°C until measurement using a sensitive and specific double-antibody cortisol assay kit (New England Nuclear), as previously described (11). The intraassay variability was 4.5%; the interassay variability was 6.6% for values in the region of 20 μg/dl and 8.4% and 9.7% for values in the region of 4 μg/dl. The minimum detectable cortisol concentration was 0.2 μg/dl of plasma. Plasma dexamethasone concentration was assayed in the laboratory of Dr. W.A. Meikle by a method previously described (12). All samples were analyzed in the same batch. The intraassay variability was less than 10%.

Statistical tests used included Pearson's method for correlation coefficients. Intergroup comparison of parametric data used means, standard deviations, and two-tailed t tests. The contributions of age and relative weight to the variance in plasma cortisol concentrations were assessed by using the standard sums of squares.

RESULTS

Postdexamethasone cortisol concentrations are shown in table 1. There was no statistically significant relationship between the predexamethasone 9:00 a.m. baseline plasma cortisol level and age (r=.0008, N=56). After dexamethasone administration, however, a significant relationship emerged between age and cortisol concentrations at 8:00 a.m. (r=.34, N=56, p=.01), 12:00 noon (r=.40, N=57, p=.002), and 4:00 p.m. (r=.29, N=55, p=.03). The relationship between age and postdexamethasone plasma cortisol level at 4:00 p.m. was similar in men (r=.32, N=32) and women (r=.32, N=23). Representative data shown in figure 1 suggest that the relationship between age and postdexamethasone cortisol concentrations was nonlinear; the rise in cortisol concentration increased with age. Only five (3%) of the 167 postdexamethasone values were above 5 μg/dl; all of these occurred in three (5%) of 56 subjects who were all 54 years old or older. There was no 8:00 a.m. postdexamethasone value greater than 5 μg/dl. Two elevated cortisol values occurred at 12:00 noon and three at 4:00 p.m. Thus, the nonsuppression rate at 4:00 p.m. was three of 55, or 5% (the 4:00 p.m. postdexamethasone cortisol value for one subject was excluded from statistical analysis). To reduce the false-positive rate to zero, a cortisol criterion of at least 9 μg/dl would be required (figure 1).

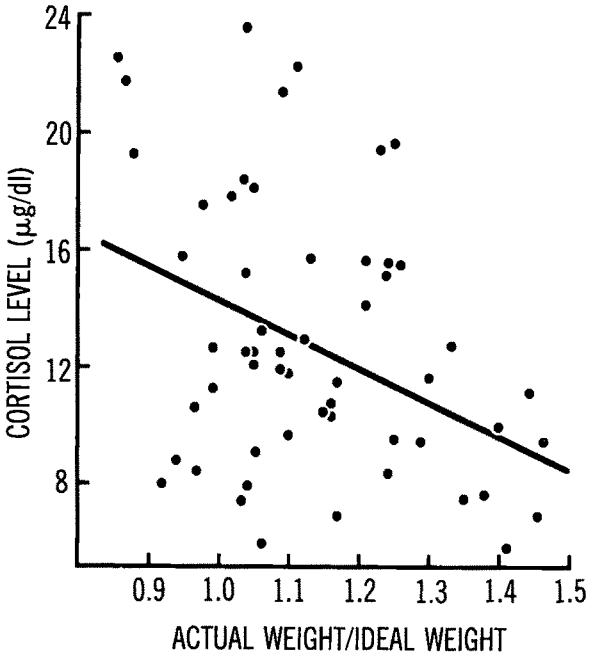
FIGURE 1. Relationship of Log Age to 4:00 p.m. Cortisol Level After Administration of 1 mg of Dexamethasone to 55 Normal Subjects[a]



[a]y=−2.53+1.125x, r=.27, p=.048.

No relationship was found between absolute body weight and 4:00 p.m. postdexamethasone cortisol level (r=.15, N=55, p=.27), indicating that a fixed dose of dexamethasone is appropriate for testing subjects of different body size. Using a relative weight index calculated by dividing subjects' actual weight by their ideal weight according to height and sex (13), we found no relationship between relative weight and age

FIGURE 2. Relationship of Relative Weight to 9:00 a.m. Baseline Cortisol Level in 56 Normal Subjects[a]



[a]y=25.66+(−11.17x), r=−.36, p=.006.

(r=.14, N=60, p=.28) but a significant inverse relationship between relative weight and baseline (predexamethasone) cortisol level (figure 2). There was also a significant inverse relationship between relative weight and 4:00 p.m. postdexamethasone cortisol level (r=−.27, N=55, p=.047). Mean±SD relative weight did not differ between suppressors (1.13±0.15) and nonsuppressors (1.02±.16) (t=1.29, df=58, n.s.).

Consideration of both age and relative weight explained more of the variance in cortisol values than was accounted for by age alone at 12:00 noon and 4:00 p.m. At 12:00 noon, age explained 16.7% of the variance (F=11.05, df=1,53, p=.0016); relative weight, 6.8% (F=4.01, df=1,53, p=.0502); and a model considering both, 28.3% (F=10.65, df=2,52, p=.0001). This multiplier effect occurred because of a differing effect of relative weight at different ages. At 4:00 p.m., the values were age, 8.4% (F=4.88, df=1,53, p=.0315); relative weight, 7.2% (F=4.13, df=1,53, p=.047); and combined, 19.1% (F=6.14, df=2,52, p=.004).

All subjects who indicated that they smoked one or more cigarettes a day were classified as smokers; those who drank a cup or more of coffee or tea each day were classified as stimulant drinkers. Only seven (12%) of 60 subjects were smokers. There was no relationship between smoking status and age, baseline cortisol levels, or postdexamethasone cortisol concentrations. Most of the subjects (47 of 59) drank coffee or tea, but drinking of stimulant beverages declined with age (t=2.29, p=.03). A t test showed no relationship between reported coffee or tea drinking and baseline or postdexamethasone cortisol values.

DISCUSSION

In a well-characterized group of normal volunteer subjects recruited from the community, age and relative weight were found to influence plasma cortisol concentrations significantly during a 1-mg DST. The influences of older age and lower relative weight in raising postdexamethasone plasma cortisol concentrations were of moderate magnitude, accounting for about a fourth of the variance. The present investigation demonstrates a trend toward higher plasma cortisol levels in older healthy, nonhospitalized control subjects, particularly those older than 65. This finding is consistent with a previous study using 0.5 mg of dexamethasone (3) and another using 1 mg (5). Another report using 1 mg of dexamethasone (14) described two- to threefold higher cortisol concentrations in elderly (65–85 years old) than in young (25–35 years old) men, but this difference did not reach statistical significance. Two series failing to demonstrate age correlations (15, 16) included relatively few elderly subjects (six of 49 subjects in one study and eight of 77 subjects in the other were older than 60), compared with our present report (23 of 56 subjects were 60 years old or older) and the other positive studies (10 of 20 subjects in one study [14] and 10 of 24 subjects in the other [3]). Thus, when noninstitutionalized elderly are well represented, they appear to have less effective suppression of cortisol after dexamethasone administration than do younger subjects.

Our finding of the relative failure of dexamethasone to produce feedback inhibition is also consistent with lower glucocorticoid effects in other systems in aging humans and other mammals (17–19). Recent weight loss and extreme obesity may be associated with cortisol nonsuppression, but moderate differences in body habitus significantly influenced postdexamethasone cortisol levels in this normal population.

Higher relative weight correlated inversely with all plasma cortisol concentrations measured, reaching independent statistical significance for the baseline and 4:00 p.m. postdexamethasone samples but contributing substantially to explanation of the variance at other times. A multicenter collaborative study failed to demonstrate a relationship between postdexamethasone cortisol measures and unadjusted weight in normal volunteers (20), but weight not corrected for height is a rather crude representation of body proportions. Ideally, somatic comparability should be maximized among subjects in whom endocrine differences due to psychiatric disease are being sought. The term "relative weight" represents thinness or obesity and takes into account the difference in body density between men and women, permitting more valid comparisons among subjects of different height and sex.

The fact that weights were adjusted for height in the present series but not in the collaborative study may explain the lack of correlation of weight and cortisol values in the latter.

Relative weight is not an ideal measure of body composition (21), but precise measures of adiposity may not be practical at the time the DST is used to determine if depression is present, and subjects' relative weight can easily be obtained from their height, weight, and the Metropolitan Life Insurance tables (13).

The absence of an effect of habitual coffee and tea consumption on plasma cortisol concentrations may indicate that the previously reported stimulation of cortisol by caffeine was due to the high dose of caffeine or the previous abstinence period imposed on those subjects (22). Although the correlations we found between age, relative weight, and cortisol level were obtained in subjects free of depression and dementia (indicating that age and body proportions independently influence cortisol feedback), these factors may not confound the DST in major depression in a simple way. Older age, weight loss, and disordered hypothalamic-pituitary-adrenal activity often coexist in major depression. In what way they are related is not known, but the relative leanness of melancholically depressed persons may contribute to higher postdexamethasone cortisol concentrations. Understanding of the mechanism of nonsuppression may shed light on the pathophysiology of melancholic depression and other conditions associated with cortisol nonsuppression after dexamethasone administration. The present data increase our understanding by confirming one and establishing another physiological factor of significance in determining cortisol suppressibility.

CONCLUSIONS

The present data demonstrate that age and relative weight influence plasma cortisol levels following dexamethasone administration in healthy, drug-free, noninstitutionalized adults with no current or previous depressive illness. The effect of age appears to be greater in old age. This apparent increase can be established more firmly by extending the present series to include more elderly subjects. We hope that the present information will also contribute to our understanding of the biological concomitants of the depressive syndrome.

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Past Sexual Victimization by Females of Male Patients in an Adolescent Medicine Clinic Population

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In an adolescent medicine clinic with more than 1,000 patients during 1982–1984, 11 male adolescents reported a history of sexual molestation by females. This molestation had commonly involved acquaintances and was unlikely to have been accompanied by threats of violence or physical coercion. One-fourth of the victims of both male and female molesters described themselves as sexually dysfunctional, and eight of the victims of male molesters identified themselves as homosexual. Both groups experienced the molestation as highly traumatic.

(Am J Psychiatry 1987; 144:650–652)

Until very recently, the following beliefs have been widely held among professionals and the lay public: that male victims of sexual molestation are uncommon, that female molesters of boys are extremely rare, and that the traumatic psychological impact on boys of sexual molestation is not very severe. With increasing media and professional attention to the problem of sexual molestation of children and to the dynamics and history of the sex offender, considerable numbers of male victims and increased numbers of cases of female molesters have been discovered almost inadvertently. Further, several studies have suggested the potentially traumatic and long-lasting impact of sexual molestation of boys (1–3). Nonetheless, research on female molesters and on male victims remains limited. A comprehensive review by Finkelhor (2) of the theoretical and clinical literature on sexual abuse of children paid special attention to the young male victim, the female molester, and long-term effects. Our study was an attempt to add to the information on these aspects of sexual abuse of children.

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METHOD

The Division of Adolescent Medicine of the New Jersey Medical School's Department of Pediatrics provides outpatient services to about 500 male adolescent patients each year. They visit the clinic for a variety of physical and psychosocial complaints and posthospitalization care. Most of the male adolescents are seen by the same male health care provider at each visit.

During the first or second clinic visit, each patient has a complete physical examination, which is preceded by an interview conducted by the examining health care provider. A complete medical and psychosocial history is obtained, and the following questions are asked: 1) Are you sexually active? 2) If you are active, are you sexually active with individuals of the same sex, the opposite sex, or both sexes? 3) Have you ever been raped, sexually abused, or forced to engage in a sexual act? 4) Are you satisfied with your current sexual status? In the event a youngster reports a history of sexual victimization, details are obtained about the molester, the actual experience(s), and the self-perceived acute and long-term impact. Counseling is provided as needed.

In a survey of all adolescent male patients seen in the clinic from 1982 to 1984, 11 cases of molestation by females and 14 cases of molestation by males were identified. We selected for comparison a control group of 25 subjects from an age-matched sample of patients who denied molestation experiences. A chi-square contingency table was used to test the statistical significance of our findings; significance was assumed at the .05 level.

In an earlier stage of our study, demographic, health, and psychosocial data were collected on 40 male adolescents seen between 1976 and 1982 who reported having been sexually assaulted by other males before puberty (1). On the basis of our earlier findings, more detailed information was obtained about the molestation experience and its impact in the most recent series of cases.

RESULTS

The characteristics of the two study groups and the control group are depicted in table 1. The female-

TABLE 1. Age and Ethnic Group of Boys Who Were Victims of Sexual Molestation and Control Subjects

Group	Age at Time of Reporting (years)		Age at Time of Molestation (years)		Subjects' Ethnic Group					
					Black		Hispanic		Caucasian	
	Mean	Range	Mean	Range	N	%	N	%	N	%
Boys molested by females (N=11)	18.2	14–24	11.9	5–17	6	55	2	18	3	27
Boys molested by males (N=14)	18.2	15–24	10.0	4–16	11	79	1	7	2	14
Unmolested control subjects (N=25)	18.4	15–23			20	80	4	16	1	4

TABLE 2. Sexual Identity and Sexual Dysfunction in Boys Molested by Females or Males and in Unmolested Control Subjects

Measure	Boys Molested by Females (N=11)		Boys Molested by Males (N=14)		Unmolested Control Subjects (N=25)	
	N	%	N	%	N	%
Sexual identity						
Heterosexual	8	72[a]	6	43[b]	23	92
Homosexual/ bisexual	3	28[a]	8	57[b]	2	8
Sexual dysfunction						
Yes	3	21[c]	4	28[d]	1	4
No	8	79[c]	10	72[d]	24	96

[a]Different from control subjects (χ^2=2.37, contingency coefficient= 0.25, df=1, p=.12).
[b]Different from control subjects (χ^2=11.37, contingency coefficient=0.48, df=1, p=.0007).
[c]Different from control subjects (χ^2=4.19, contingency coefficient= 0.32, df=1, p=.04).
[d]Different from control subjects (χ^2=4.85, contingency coefficient= 0.33, df=1, p=.03).

molested group and the male-molested group were of comparable age at the time of the initial visit to the clinic. The female-molested group was slightly but not significantly older at the time of the molestation. A striking demographic difference was found between the victims of female and male molesters: twice as many of the victims of female molesters were Hispanic or Caucasian.

The mean age of both male and female molesters was 26 years, with an age range of 16–36 years for female molesters and 15–45 years for male molesters. The female molesters were usually acquaintances of the victims—most often a neighbor, baby sitter, or other trusted older adolescent or young adult. The 14 male molesters were nearly equally divided among relatives, acquaintances, and strangers.

The molestation by both male and female molesters involved a variety of sexual acts, including fondling, mutual masturbation, and oral, anal, and genital activities. Multiple types of acts were common. The vast majority of the female molesters used persuasion rather than physical force or threats (10 of 11 cases). Three-quarters of the female molesters attempted to get their victims to ejaculate, and nearly half succeeded. Although the percentage of male-molested victims who reported the incident (36%, N=5) was double the percentage of female-molested victims who reported the incident (18%, N=2), this difference did not reach significance in our sample (χ^2=0.94, contingency coefficient=0.19, df=1, p=.33).

The current sexual identity and sexual dysfunction of the study groups and the age-matched control group are depicted in table 2. Sexual dysfunction was defined as nonorganically based complaints of inhibition of libido, premature ejaculation, erectile difficulties, and failure to ejaculate. Our findings with the most recent group of male-molested boys (N=14) confirmed our findings with the earlier group (N=40): approximately one-half of the boys who had been molested by males currently identified themselves as homosexual and often linked their homosexuality to their sexual victimization experience(s). The female-molested group, in contrast, seemed no more likely to identify themselves as homosexual than the control group of unmolested adolescents. They did have a higher rate of the sexual dysfunctions we mentioned.

With regard to the effect of the sexual molestation—both the recollection of the immediate impact and the current self-perceived impact on the victim's life—no significant differences were noted between the male-molested and the female-molested groups. The majority of both groups experienced the molestation as having had an intense traumatic impact on their lives at the time of the experience and at the time of reporting several years afterward. On a 4-point scale ranging from devastating to strong to some effect to not much effect, 73% of the female-molested boys (eight of 11) and 64% of the male-molested boys (nine of 14) recalled the immediate impact as strong or devastating (χ^2=0.20, contingency coefficient=0.09, df=1, p=.65). At the time of reporting, 54% of the female-molested boys (six of 11) and 50% of the male-molested boys (seven of 14) continued to rate the experience as having a strong or devastating effect on their lives (χ^2=0.05, contingency coefficient=0.05, df=1, p=.82).

DISCUSSION

Our identification of 11 male adolescents who had been molested by females during the same 2-year period in which we identified 14 adolescents who had been molested by males suggests that molestation by females is far from being an uncommon experience. Our retrospective findings are similar to the findings of Fritz et al. (4), who found that of the 4.8% of male undergraduate psychology students who reported child-

hood sexual victimization, 60% had been molested by females. These percentages of female molesters of boys were considerably higher than those found in other retrospective surveys by Finkelhor (15% and 16%) (2, 5), Bell and Weinberg (27% and 14%) (6), and Gebhard et al. (27%) (7).

We are reluctant to estimate the incidence and prevalence of sexual molestation by either males or females in our adolescent medicine population of approximately 500 patients per year. We are convinced that the adolescents who admit having been sexually victimized represent only a portion of the true numbers, if for no other reason than that no boy under the age of 14 years and few under 17 years admitted having been molested, despite the fact that most of the reported molestations had occurred before the boys reached puberty. We are unable to explain this failure of early adolescents to admit to childhood sexual molestation experiences. We can only speculate that either they are uncomfortable about their sexuality in general—guilty and anxious about the meaning of the experience, still too young to have developed some perspective—or they repress and deny the experience until they reach a level of maturity at which they are more capable of dealing with it.

We wish to emphasize the confirmation of our earlier finding that there is a high rate of self-identification as homosexual among the victims of male molesters. Approximately one-half of the current (N=14) and previous (N=40) study groups claimed to be homosexual. These findings are further confirmed by Finkelhor's 1979 college student survey, in which nearly half of the males who reported "a childhood sexual experience with an older man were currently involved in homosexual activity" (5). We would agree with Finkelhor's impression that the boy who has been molested by a man may label the experience as homosexual and misperceive himself as homosexual on the basis of his having been found sexually attractive by an older man (2), particularly if he has had no opportunity to be reassured and relieved of his guilt and anxiety about his role in the molestation experience. Once self-labeled as homosexual, the boy may then place himself in situations that leave him open to homosexual activity. It should be emphasized that the vast majority of homosexual men do not report childhood sexual experiences, and the vast majority of male pedophiles do not regard themselves as homosexual.

The victims of both female and male molesters appear to be at increased risk for sexual dysfunction, as has previously been noted by those working with adult female rape victims (8). The marked anxiety and feelings of helplessness and guilt described by many victims of sexual abuse, including our own study groups, appear to be reawakened by attempts at later sexual activity.

We believe that our finding that the majority of our male- and female-molested subjects experienced the molestation as strongly or devastatingly traumatic is quite important. Our group represented a community-based sample not drawn from mental health, social service, or criminal justice sources. None of our study group members had reported their sexual abuse to the police or to a hospital or clinic with a sexual abuse facility, nor did sexual abuse represent their chief complaint in the adolescent medicine clinic. Therefore, the traumatic impact of their experiences cannot be attributed to the interventions of any protective, health, or mental health agencies. The nature of the traumatic impact needs to be further explored. It is our impression, however, that the vast majority of our study group are functioning well overall and are asymptomatic with the exception of mild to moderate impairments in the areas of sexual identity, sexual functioning, self-esteem, and interpersonal relationships. The impairments are often subtle but nonetheless disturbing to the individual. On the basis of our data, we strongly support those who believe childhood sexual victimization, whether by male or female molesters, is a high-risk experience that markedly increases the likelihood of acute and future disturbances in important areas of functioning (9–11).

We recommend including questions about childhood sexual experiences as part of the routine intake evaluation for pediatric and child psychiatric clinical populations and as part of a sexual history during evaluations of adult patients.

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Separation Anxiety and School Phobia: A Comparison Using *DSM-III* Criteria

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Children who met DSM-III *criteria for separation anxiety disorder (N=48) or a phobic disorder of school (N=19) were compared with respect to demographic characteristics, symptoms, associated psychiatric disorders, and maternal psychiatric illness. More children with separation anxiety disorder were female, prepubertal, and from families with lower socioeconomic backgrounds. Children with separation anxiety disorder were less likely to exhibit school refusal than children with school phobia. However, they were more likely to meet criteria for an additional* DSM-III *diagnosis. Finally, their mothers had a rate of affective disorders four times greater than that of mothers of children with school phobia.*

(Am J Psychiatry 1987; 144:653–657)

The term "school phobia" first was introduced in the clinical literature by Johnson et al. (1) in 1941. The term was used to denote a syndrome of childhood characterized by marked anxiety about attending school and absenteeism. The syndrome was thought to be precipitated by fear of leaving the mother or home rather than a fear of school per se. In fact, Estes et al. (2) later substituted the term "separation anxiety" to communicate better the focus of pathology. Similarly, Bowlby (3) has maintained that the school phobic child fears the absence or loss of an attachment figure (i.e., mother) or security base (i.e., home) rather than fearing and avoiding the actual school situation, as a truly phobic individual would. He has suggested that the term "pseudophobia" be used to help clarify the underlying pathological processes involved.

Alternatively, other investigators (4) have favored a fear-of-school hypothesis, where the child is viewed as having a phobic reaction to some aspect of the school environment. In general, however, most clinicians and researchers in this area acknowledge that anxiety about attending school can stem from separation problems *or* from excessive fear about some aspect of school itself (5).

This diagnostic confusion has been compounded further by the appearance of "separation anxiety disorder" in the most recent version of *DSM-III*. As defined in *DSM-III*, the essential feature of separation anxiety disorder is excessive anxiety concerning separation from a major attachment figure and/or home. The diagnostic criteria for the disorder include nine symptoms, only three of which must be met to receive the diagnosis. Although reluctance or refusal to go to school is included as one of the nine symptoms characteristic of separation anxiety disorder, a child need not exhibit this particular behavior to meet criteria for the disorder.

Unfortunately, historically, and even into the present, the label "school phobia" has been applied to both types of children, that is, those who evidence separation anxiety and those who show a phobic reaction toward school. However, it is clear that not all children with school phobia show separation anxiety problems, nor do all children with separation anxiety disorder exhibit school refusal. It is less clear in which ways and to what extent these two populations actually differ. Indeed, although several studies have been published on the characteristics of "school phobia," a comparison of children with separation anxiety disorder and those with a specific phobia of school has not appeared.

The purpose of this paper is to examine and compare the clinical and associated features of the two disorders by evaluating a clinical sample of children who met *DSM-III* criteria for either separation anxiety disorder or a phobic disorder (simple or social) of school. The children were assessed on a variety of dimensions, including demographic characteristics, symptomatology, associated psychiatric disorders, and maternal psychiatric illness.

METHOD

Sample

During a 20-month period (September 1984 through April 1986), 48 children with separation

Received June 9, 1986; accepted Sept. 18, 1986. From the Department of Psychiatry, Western Psychiatric Institute and Clinic, University of Pittsburgh School of Medicine. Address reprint requests to Dr. Last, Western Psychiatric Institute and Clinic, 3811 O'Hara St., Pittsburgh, PA 15213.
Supported in part by NIMH grant MH-00546.
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anxiety disorder and 19 children with a phobic disorder of school were evaluated in the Child and Adolescent Anxiety Disorder Clinic at Western Psychiatric Institute and Clinic. Patients were interviewed and diagnosed using the Interview Schedule for Children, which is a semistructured, symptom-oriented psychiatric interview based on *DSM-III* criteria (unpublished 1978 and 1983 manuscripts by M. Kovacs). Previous research by our group has shown high levels of diagnostic agreement using this instrument for a wide range of childhood psychiatric disorders, including both separation anxiety (N=28, kappa=0.81, agreement=91%) and school phobic disorders (N=10, kappa=1.00, agreement=100%) (unpublished 1986 manuscript by Last et al.).

Procedure

Prior to their diagnostic interviews, children completed several self-report anxiety measures, including the State-Trait Anxiety Inventory for Children (6), the revised Child Manifest Anxiety Scale (7), and the revised Fear Survey Schedule for Children (8). At this time, information also was collected on the following demographic variables: age, sex, and race of child and socioeconomic level of the child's family. Social class ratings were determined using the Hollingshead Four-Factor Index of Social Status (unpublished 1975 manuscript by A.B. Hollingshead).

Comorbidity was examined by observing concurrent *DSM-III* diagnoses assigned to children following their diagnostic assessments with the Interview Schedule for Children. In order to obtain a comprehensive picture of comorbidity, the *DSM-III* hierarchical system and diagnostic exclusionary rules were not adhered to as they pertain to the diagnosis of anxiety and affective disorders. In other words, children were assigned all the *DSM-III* anxiety and affective diagnoses for which they qualified.

Thirty-five (73%) of the 48 mothers of children with separation anxiety disorder and 14 (74%) of the 19 mothers of children with school phobia were interviewed about their own psychiatric histories with the Structured Clinical Interview for *DSM-III*—Non-Patient Version (unpublished 1984 and 1985 manuscripts by Spitzer and Williams). This is a *DSM-III*-based structured diagnostic interview schedule which covers both current and past episodes of psychiatric illness. (This part of the study was initiated several months after the onset of data collection for the rest of the project. Thus, we obtained maternal psychiatric histories on about 75% of the total sample.)

Mothers were interviewed by a clinician who was blind to patients' diagnoses. Interrater reliability for the mothers' diagnoses was evaluated by having a second clinician, also blind to patients' diagnoses, independently score audiotapes of two-thirds of the interviews. Overall diagnostic agreement between the two clinicians was 88%. Agreement for anxiety and affective disorders was 90% and 94%, respectively.

TABLE 1. Demographic Characteristics of Children With Separation Anxiety Disorder or School Phobia

Characteristic	Children With Separation Anxiety Disorder (N=48)	Children With School Phobia (N=19)
Age (years)		
Mean	9.4	14.3
SD	2.9	2.3
Sex		
Female		
Number	33	7
Percent	69	37
Male		
Number	15	12
Percent	31	63
Race		
White		
Number	43	19
Percent	89	100
Black		
Number	5	0
Percent	11	0
Head of household's social class (Hollingshead index)		
I, II, or III		
Number	15	13
Percent	32	71
IV or V		
Number	33	6
Percent	68	29

RESULTS

Demographic Characteristics

Table 1 presents the demographic characteristics of the children with separation anxiety disorder and school phobia.

Age at intake. The two groups differed significantly with respect to age at intake ($t=6.59$, $p<.001$). Children with separation anxiety disorder were significantly younger than children with school phobia. Moreover, when the percentages of children (age less than 13 years) and adolescents (age 13 or more years) were compared, the separation anxiety disorder group showed a significantly higher percentage of children (81%) than the school phobia group (21%) ($\chi^2=18.92$, df=1, $p<.001$).

Sex. The separation anxiety disorder and school phobia groups differed significantly in their sex distributions ($\chi^2=4.51$, df=1, $p<.05$). The majority of children with separation anxiety disorder (69%) were female, while the majority of children with school phobia (63%) were male.

Race. Almost all the children in both of the anxiety groups were white (table 1). The two groups did not differ significantly with respect to racial composition.

Social class (Hollingshead index). Social class ratings were combined into two groups: 1) middle-upper socioeconomic level (I, II, and III) and 2) lower socioeconomic level (IV and V). The separation anxiety disorder and school phobia groups differed significantly in their socioeconomic level ratings ($\chi^2=4.81$,

TABLE 2. Concurrent *DSM-III* Disorders in Children With Separation Anxiety Disorder or School Phobia

Concurrent Disorder	Children With Separation Anxiety Disorder (N=48) N	%	Children With School Phobia (N=19) N	%
Any anxiety disorder	24	50.0	10	52.6
Any affective disorder	16	33.3	6	31.6
No concurrent disorder	4	8.3	7	36.8

df=1, $p<.05$). The majority of families of children with separation anxiety disorder received lower socioeconomic level ratings, while the majority of families of children with school phobia received middle-upper socioeconomic level ratings.

Concurrent Disorders

Table 2 indicates the percentage of children in the separation anxiety disorder and school phobia groups who presented with a concurrent anxiety disorder, an affective disorder, or no concurrent disorder. As can be observed, one-half of the children in both the separation anxiety disorder and school phobia groups met *DSM-III* criteria for at least one additional anxiety diagnosis. Overanxious disorder was the most frequent anxiety diagnosis for both of the groups (22 [46%] of the children with separation anxiety disorder, seven [37%] of the children with school phobia).

Approximately one-third of the children with separation anxiety disorder and school phobia received an additional diagnosis of an affective disorder. Almost all of the children who met criteria for an affective disorder were diagnosed as having major depression (15 [31%] of the children with separation anxiety disorder and five [26%] of the children with school phobia).

Children with separation anxiety disorder overall were significantly more likely to have a concurrent psychiatric disorder than children with school phobia ($\chi^2=6.12$, df=1, $p<.05$). In fact, almost all of the children with separation anxiety disorder (N=44, 92%) received a concurrent diagnosis, compared to 63% (N=12) of the school phobia group.

Symptom Measures

Children with separation anxiety disorder and school phobia did not differ significantly on the State-Trait Anxiety Inventory for Children, the Child Manifest Anxiety Scale, or the revised Fear Survey Schedule for Children. The two groups also were compared on the Interview Schedule for Children interviewer ratings for school refusal. Results from this measure indicated that children with school phobia were more likely than children with separation anxiety disorder to present with school avoidance (35 [73%] of the children with separation anxiety disorder and all of the children with school phobia) ($\chi^2=4.74$, df=1, $p<.05$).

TABLE 3. *DSM-III* Anxiety and Affective Disorders in Mothers of Children With Separation Anxiety Disorder or School Phobia

DSM-III Diagnosis	Mothers With Diagnosis: Mothers of Children With Separation Anxiety Disorder (N=35) N	%	Mothers of Children With School Phobia (N=14) N	%
Any anxiety disorder	29	82.9	8	57.1
Any affective disorder	22	62.9	2	14.3
No disorder	5	14.3	5	35.7

In order to determine whether differences between the separation anxiety disorder and school phobia groups were due to the presence or absence of school refusal, we compared children with separation anxiety disorder who exhibited school avoidance with those who did not. There were no significant differences between these two groups of children with separation anxiety disorder for any of the demographic variables, concurrent disorders, or symptom measures.

Maternal Psychiatric Illness

The rates of anxiety and affective disorders for mothers of children with separation anxiety disorder and school phobia are presented in table 3. As indicated, the majority of mothers in the separation anxiety disorder and school phobia groups had a lifetime history of at least one anxiety disorder. The most frequent anxiety diagnosis for mothers of children with separation anxiety disorder was generalized anxiety disorder (N=17, 49%), while the most frequent diagnoses for mothers of children with school phobia were simple phobia (N=3, 21%) and generalized anxiety disorder (N=3, 21%).

Mothers of children with separation anxiety disorder were significantly more likely to have a lifetime history of an affective disorder than mothers of children with school phobia ($\chi^2=7.6$, df=1, $p<.01$). In fact, the majority of mothers of children with separation anxiety disorder received a diagnosis of an affective disorder, compared to only two of the mothers in the school phobia group. Of the mothers of children with separation anxiety disorder who met criteria for an affective disorder, almost all (N=19, 86%) received the diagnosis of major depression.

Very few mothers in the separation anxiety disorder group (14%) did not receive a lifetime psychiatric diagnosis, compared to 36% of the mothers in the school phobia group. This difference, however, was not statistically significant.

The rate of current anxiety disorders also was examined for mothers in both of the groups. Over one-half of mothers of children with separation anxiety

disorder (N=20, 57%) presented with an anxiety disorder at the time of their diagnostic interviews, compared to 29% (N=4) of mothers of children with school phobia. This difference, however, was not statistically significant.

DISCUSSION

Findings from the present study highlight several important differences in the clinical and associated features of separation anxiety disorder and school phobic disorder. Children with the two disorders were distinguishable by their demographic characteristics, presence or absence of a concurrent psychiatric disorder, and presence or absence of school refusal. Moreover, the mothers of children in the two groups differed in their lifetime psychiatric histories, specifically with respect to the affective disorders.

Previous studies with "school phobic" children, which did not employ *DSM-III* criteria or distinguish children with separation anxiety from those with phobic disorders, have produced inconsistent results with respect to demographic characteristics (9). By contrast, in our study, where children were carefully diagnosed and distinguished using *DSM-III,* analysis of demographic variables revealed that children with separation anxiety disorder and school phobia represent two distinct populations. Children with separation anxiety disorder generally are female, prepubertal, and from families of lower socioeconomic status, while children with school phobia tend to be male, postpubertal, and from higher socioeconomic backgrounds.

We also found that children with separation anxiety disorder overall were more likely than children with school phobia to receive an additional *DSM-III* diagnosis. Indeed, virtually all of the children with separation anxiety disorder (92%, N=44) met criteria for at least one concurrent disorder, compared to 63% (N=12) of the school phobia group. This difference suggests that children with separation anxiety disorder are more severely disturbed than children with school phobic disorder, in that they almost always manifest sufficient additional psychopathology to warrant a second diagnosis.

There was some suggestion that mothers of children with separation anxiety disorder, like their offspring, are more severely disturbed than mothers of children with school phobia. In this regard, the most striking finding was the rate of affective disorders (which in almost all cases consisted of major depression) for mothers in the separation anxiety disorder group, a rate four times greater than that obtained in the school phobia group. In addition to underscoring the extent of psychopathology in this group of mothers, the high prevalence rate of major depression in mothers of children with separation anxiety disorder provides indirect support for the previously hypothesized relation between separation anxiety disorder and major depression (10–12).

It is of interest that none of the three anxiety questionnaires administered to the children yielded significant differences between the two groups. In retrospect, one might not expect differences between children with separation anxiety disorder and school phobia on the State-Trait Anxiety Inventory for Children and the Child Manifest Anxiety Scale, since these essentially are global indices of anxiety. The revised Fear Survey Schedule for Children, on the other hand, is a measure of specific fears. *DSM-III* suggests that separation anxiety disorder is characterized by a wide range of feared situations, all of which are related to separation concerns (e.g., fear of going to school, fear of being home alone, fear of going out alone, etc.). Alternatively, the diagnostic criteria for simple phobia suggest that the range of feared situations is restricted or relatively well circumscribed. Thus, we anticipated that children with separation anxiety disorder would report a greater array of extreme fears on the Fear Survey Schedule than children with school phobia. In fact, we did find that children with separation anxiety disorder, on the average, endorsed a greater number of intense fears (18 fears) than children with school phobia (11 fears). This difference, although clinically meaningful, was not statistically significant, most likely due to the relatively small size of the school phobia group.

As expected, children with separation anxiety disorder were significantly less likely to exhibit school refusal than children with school phobia. Thus, although most children with separation anxiety disorder show school avoidance (73% in this sample), the behavior is not necessary for receiving the *DSM-III* diagnosis, nor is it evident in all cases of the disorder.

We also wish to point to the relatively large difference in the prevalence of the two childhood anxiety disorders observed at our outpatient anxiety clinic. As indicated by the numbers of children who met *DSM-III* criteria for each of the two groups, our preliminary data suggest that the rate of separation anxiety is nearly two-and-one-half times greater than that of school phobic disorder.

In summary, results from our investigation indicate that separation anxiety disorder and school phobic disorder differ on a number of dimensions, thus supporting the use of *DSM-III* criteria for differentially diagnosing the two anxiety disorders. The implications of these findings for the treatment of these disorders await empirical evaluation.

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Folie à Famille: Shared Paranoid Disorder in a Vietnam Veteran and His Family

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Reports of folie à famille are rare; this may be the first reported case involving a Vietnam veteran. Expression of his paranoid schizophrenia involved delusions and hallucinations relating to Vietnam, and his wife and children shared his paranoia. Typical of folie à famille were the dominant family member, the threat of violence, and the family's social isolation, frequent crises, and stable membership. Although the veteran's intrusive recollections of his Vietnam experience were typical of posttraumatic stress disorder, he acted on rather than avoided them. Treatment focused on the entire family, partly to minimize future problems in the children.

(Am J Psychiatry 1987; 144:658–660)

The occurrence of "a persecutory delusional system that develops as a result of a close relationship with another person who already has a disorder with persecutory delusions" (*DSM-III*, p. 197) is rare. Shared paranoid disorder most often consists of folie à deux. Early interest in such dyads produced a clear definition and classification of subtypes before the turn of the century (1–5). Shared paranoid disorder in which the delusions are shared beyond a simple dyad are even less common. This is the "folie à famille"; approximately 20 cases have been reported (6–17). It is noteworthy that among the many families exposed to the delusional systems of their members, these delusions are rarely shared. Even in families including two or more schizophrenic patients, delusions are usually not "communicated" or "transmitted" and do not become shared.

There seem to be six typical features of families who develop folie à famille: 1) these families are socially isolated, 2) family relationships tend to be mutually dependent and ambivalent, 3) the families are repeatedly in crisis (15), 4) there is often an underlying threat or the frank presence of violent behaviors, 5) the family membership is stable over a long period of time, and 6) there is a dominant family member, the inducer, around whom the delusional beliefs evolve. The other family members, the induced, are often less intelligent, female, and passive, dependent, suggestible, or histrionic (10, 14, 15).

The delusions are most commonly of a paranoid nature. Typically, the inducer believes himself to be the object of persecution, and gradually the focus shifts to include the entire family (9, 13–15).

It has been suggested (6, 18) that cases of shared delusions in families may be more common than the literature reflects. Such families are unlikely to seek treatment. In most reported cases, family members were brought to treatment by outsiders because of bizarre or violent behavior (10, 11, 14).

Vietnam veterans suffer from many of the factors associated with the development of folie à famille. This group of veterans returned from war to be received by society with great ambivalence (19, 20). They tend to be alienated from society and socially isolated. Their family relationships are often ambivalent, and violence is not uncommon. There has been much written regarding posttraumatic stress disorder in Vietnam veterans, including the difficulty in distinguishing posttraumatic stress disorder from other disorders, such as affective disorders (21), factitious disorders (22), antisocial personality disorder (23), and even paranoid schizophrenia (24). However, we are unaware of prior reports of shared paranoid disorder in this patient group. We describe a case of shared paranoid disorder involving the wife and three children of a Vietnam veteran.

CASE REPORT

The Inducer

Mr. A, a 37-year-old Mexican-American Vietnam veteran previously treated at several Veterans Administration hospitals with the diagnosis of paranoid schizophrenia, came to the emergency room stating, "My life is in danger." His wife accompanied him, and both wore combat fatigues. Mr. A told a semicoherent story of international spy intrigue that was built around the release of soldiers still missing in action or held as prisoners of war in Vietnam. He believed he was hunted by Vietnamese agents. He was unable to sleep

Received Dec. 30, 1985; revised May 12 and Aug. 29, 1986; accepted Nov. 5, 1986. From the Department of Psychiatry, University of California, San Diego, School of Medicine; and the Department of Psychiatry, San Diego VA Medical Center. Address reprint requests to Dr. Glassman, Department of Psychiatry, University of California, San Diego, Gifford Mental Health Clinic, 3430 Fifth Ave., San Diego, CA 92103.

without the protection of a shotgun propped against the door and a loaded revolver under his pillow.

Mr. A reported hearing the voices of the men from his company who died during the Tet offensive. These voices tended to severely criticize and chastise him. He had become so disturbed by these beliefs and auditory hallucinations that he made suicidal efforts to escape the torment.

Mr. A contended he had traveled to Europe for meetings with people who knew the whereabouts of unreturned prisoners of war and soldiers missing in action. He produced a business card identifying him as the regional commander of a Vietnam veterans' organization dedicated to recovery of prisoners of war, and then he named a retired United States Marine Corps general who coordinated such volunteer efforts. This general was contacted, and he substantiated Mr. A's attendance at these meetings. He indicated that Mr. A's involvement in these matters was peripheral and that no one would consider him to be sufficiently important to wish him harm.

The Induced

As part of the evaluation, meetings were held with Mr. A and his wife and with the whole family. Mrs. A visited her husband daily from the beginning of her husband's hospitalization, often accompanied by their children—two boys, age 14 and 12, and a girl, age 15. The couple had been married 16 years. Mrs. A was an attractive Catholic Salvadoran woman, and often dressed in a flamboyant and suggestive manner. She would focus only on the very complicated and involved conspiracies involving the prisoners of war. She tended to speak in a disorganized and vague manner.

Mr. A had married his wife soon after his return from Vietnam. It had been a chaotic and unusual life. Mr. A had been treated at many VA hospitals and was usually diagnosed as paranoid schizophrenic, but he was never treated at the same center more than once. He moved the family repeatedly, as he became suspicious of the people in each place. They often lived in remote, isolated settings. Mr. A's behavior was unpredictable. He would leave home for days, usually involved in some imagined conspiracy involving the soldiers missing in action. Mrs. A often had to find him in some distant city, usually in the psychiatric ward of a new VA hospital.

As Mrs. A shared more information with us, she admitted to frequent marital fights, sometimes involving the threatened use of weapons. The younger son had learned to "hide the kitchen knives when Mom and Dad fought." Mrs. A admitted, "Sometimes he dreams dreams that cannot be for me," referring to his recent plan to move the family to Laos to enable him to fight the Vietnamese communists. He intermittently accused her of seeing other men, becoming angry and jealous. She was unwilling to leave him, explaining that he was the father of her children.

Although Mrs. A had some awareness of the fantastic quality of her husband's beliefs, it became clear that Mrs. A and the children shared Mr. A's paranoid viewpoint. Most problematic was the family's belief that they were in danger. The older son had been trained by Mr. A in karate and the use of shotguns to defend the household against "any Oriental who comes near." The family believed they were discriminated against by segments of society: the school system, neighbors, landlords, the health care system. The daughter's attendance at school was sporadic. She seemed to be markedly quiet and withdrawn and had an apparent school phobia. Both she and Mrs. A felt that she was persecuted.

Treatment Course

The results of Mr. A's physical examination and laboratory screening were unremarkable, and he did not use alcohol or street drugs. He was given haloperidol and soon was less hypervigilant and less bothered by auditory hallucinations. However, his delusions persisted.

Feelings of isolation, alienation, and suspiciousness persisted in all the family members. As the family seemed to be increasingly engaged with the treatment team, we began to suggest that Mr. A's guns be removed from the house. The family members uniformly resisted this idea. It was Mr. A who finally helped convince his family to remove the guns, saying that perhaps he had been "blowing some things out of proportion."

Treatment seemed to go well. Although Mr. A continued to be guarded and vague, he was less overtly psychotic. The family continued to meet with us, and Mrs. A gradually became less preoccupied with the conspiracies and started to focus on real family issues, such as housing and the children's social and educational problems. She had one individual session with the team's social worker to discuss possible interventions.

The night after that meeting Mr. A left the hospital, leaving no word, and did not return. The family had no telephone; we sent them a letter but received no response. We visited their home and found them in a tiny one-bedroom alley apartment in a poor immigrant neighborhood. Mrs. A received us warmly, Mr. A with some reluctance. The guns were still out of the house, although they had been replaced by a watchdog that Mr. A reported was "always awake." Mr. A had not taken his haloperidol for 2 weeks, and both he and his wife were again immersed in their world of conspiracies. He asked for haloperidol because it made him "less nervous," and they agreed to continue in outpatient treatment. They did keep one outpatient appointment and telephoned once.

Our next contact came several months later, when Mr. A was hospitalized. He had become catatonic briefly after his mother died and his brothers claimed that he had not done enough for her during her illness. He was again disorganized and delusional, and his wife was less so. Their daughter had dropped out of school, feeling too uncomfortable there, and was spending her days at home with her parents. She had also attempted suicide by taking an overdose of aspirin. Mr. A had refused to bring her for treatment, saying "all she'll get is a label." After his admission for catatonia, he again left the hospital precipitously and did not return.

DISCUSSION

This exemplifies most of the features of folie à famille. Social isolation, frequent crises, and stable family membership over time were all present. There was certainly the presence, and constant threat, of violent behavior. In Mr. A there was a dominant family member, an inducer, with a major psychiatric illness. As is most often the case, the delusions were of a persecutory nature. In this family the marital relationship seemed central to the development of the

shared delusional system. Mrs. A shared her husband's life and his delusions.

The situation of the children raises other issues. The roles of genetic and environmental factors (25) and the developmental, ethical, and legal issues cannot be fully elaborated in this report. We were particularly concerned about the daughter, who seemed to be developing major psychopathology, possibly schizophrenia. All three children had been raised in isolated, chaotic environments and were frequently exposed to violent behavior, although there was no evidence or history of direct child abuse and the children's basic needs appeared to have been met. However, it is not always clear at what point such circumstances constitute neglect. Partly because of the vulnerability of the children, we made great efforts to engage the entire family in treatment in hopes that the existence of a therapeutic alliance would at least offer the potential for prevention of, or help with, future problems.

Mr. A's clinical picture had some features of *DSM-III* posttraumatic stress disorder. The content of his delusions was related to Vietnam, and he did have "intrusive recollections of the event." However, rather than showing "numbing of responsiveness" or "reduced involvement with the external world," he was responsive and involved with the world, although in a bizarre, disorganized, and delusional way. Rather than avoiding "activities that arouse recollection of the traumatic event," he was preoccupied with such activities. An integrative model more accurately represents his illness. The stress of Vietnam combined with his premorbid characteristics in such a way that the expression of his schizophrenia involved delusions and hallucinations relating to his Vietnam experience.

The family, especially Mr. A, could not tolerate the increasing involvement and closeness with the treatment team. It has been suggested (26, 27) that treatment of folie à deux should involve separation of the induced from the inducer and that, once separated, the induced will revert to normalcy. This has not been found to be universally the case (12). Our experience with this family suggests that only by involving the entire family can there be any hope for successful intervention. Development of trust and a therapeutic alliance is difficult and must be gained gradually with the entire family.

Finally, we wish to emphasize the importance of family involvement in the assessment and treatment of the psychiatrically disturbed Vietnam veteran. Mr. A had had several hospitalizations, yet the family had never been seen, and the folie à famille had never come to light. Wikler (6) and Stierlin (18) have commented that all families share certain beliefs, myths, and interpretations of reality and that folie à famille may represent an extreme on a continuum. The Vietnam war has had, and continues to have, an impact on the veterans who served there and their families. This case is an extreme example. Stanton and Figley (28) and Williams and Williams (29) have written eloquently on the importance of family involvement in the treatment of Vietnam veterans. Knowledge of the family context of the disturbed Vietnam veteran can be helpful, and sometimes crucial, in assessment, treatment planning, and evaluation of interventions.

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Stressful Life Events and Psychiatric Hospitalization of Mentally Retarded Patients

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The authors compared the type and number of life events experienced by 19 mentally retarded patients and 19 nonretarded control subjects in the month before their admission to the same unit of a state mental hospital. The retarded patients had exhibited fewer changes in eating and other personal habits. On admission they presented fewer signs of intrapsychic disturbance but more of self-destruction or aggression. These results imply that clinicians need specific training to diagnose and treat psychiatric disorders in the mentally retarded patients who now use community mental health facilities, because their presentations may be atypical.
(Am J Psychiatry 1987; 144:661–663)

Since the advent of deinstitutionalization, community mental health centers (CMHCs) and psychiatric hospitals have assumed responsibility for the psychiatric care of persons with subnormal intelligence. However, most facilities are ill-prepared to deal with this new patient population and the issues of diagnosis and treatment these patients raise.

Low intelligence may increase the risk of emotional disturbance because it creates special adjustment problems while limiting the individual's ability to cope with these problems (1, 2). The actual rate of disturbance among the retarded population is unknown, but estimates in the literature range from 8% to more than 50% (3). This wide disparity in estimates may be due to the difficulty in diagnosing mental illness in this group. Several investigations on the assessment of psychopathology in retarded persons (4–8) have documented the coexistence of mental retardation and depression, schizophrenia, and a full range of other psychopathological conditions. Diagnosis of these coexistent conditions, however, is complicated by "overshadowing," in which clinicians tend to focus on the patient's intellectual deficiency rather than on signs of emotional disturbance (9, 10). Without proper diagnosis, subsequent treatment, including determination of the need for psychiatric hospitalization, may be compromised. The general dearth of information regarding dual disabilities may lead to the use of different (and possibly inadequate) criteria for determining the need for hospitalization of such persons from those applied to persons of normal intelligence.

The impetus for the present study was the observation that situations leading to hospitalization appeared to differ depending on patients' intellectual abilities. Patients with both mental retardation and psychiatric disorder appeared to have behavior problems in the home environment but showed little evidence of the intrapsychic disturbance that is the focus of most clinicians' psychiatric evaluations. In many cases the precipitating problem appeared to be the caretaker's difficulties in coping with aggressive behaviors. It also seemed possible that changes in the home environment may have contributed to the difficulties. Although psychiatric hospitalizations are situationally determined for all patients to some extent, we hypothesized that mentally handicapped patients with psychiatric disorder were more likely than other patients to be affected by environmental changes and less likely to present the typical signs of emotional disturbance with which clinicians are trained to work.

METHOD

All of the subjects in this study were hospitalized between October 1982 and June 1983 in a community-based state psychiatric center in Syracuse, N.Y. The center serves a population of 750,000. During the 8-month study period, 19 persons (about 1% of all admissions) were diagnosed as having mild, moderate, severe, profound, or unspecified mental retardation (*DSM-III* categories 317–319) at the time of admission. A 19-patient control group consisted of the next patient admitted to the same ward as the target subject, generally on the same day.

To assess environmental changes in patients' lives before their hospital admission, a checklist of 30 stressful life events was developed on the basis of previous studies of relationships between life changes

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Supported in part by a State University of New York New Faculty Development Award to Dr. Stack, Account 22001108.
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and physical or mental illness (11–13). Items on living and interpersonal situations (14 events), health and habit changes (six events), work (including sheltered workshops) and school (seven events), legal problems (two events), and vacation (one event) all apply to noninstitutionalized retarded persons.

Four other rating categories tapped behaviors likely to precipitate hospitalization. These were self-destructive behavior, person-oriented physical aggression, property-oriented physical aggression, and intrapsychic problem. The latter was scored when the patient, evaluator, or a reliable collateral source referred specifically to some symptom of intrapsychic difficulty (e.g., "depressed," "unhappy," "nervous").

After reliability testing, two experienced clinicians (C.V.H. and M.T.) used the checklist to identify occurrences in the month before the hospital admission, based on the evaluation. Only changes identified independently by both judges were accepted.

Life events and problem behaviors were rated on the basis of evaluators' accounts of patients' and informants' presentation and history. Identifying data, including statements referring to developmental disability, were removed from the forms used to the extent possible, but references to group homes in the narratives occasionally may have served to identify patients' group membership to the raters. This unavoidable problem was not thought to prejudice the data unduly. Final diagnoses and demographic data were drawn from the hospital information system.

RESULTS

The two groups of patients in the study were demographically similar. Slightly more than half of the patients in both groups were men: 11 (58%) in the retarded group and 10 (53%) in the control group. Their ages ranged from 18 to 62 years; the mean age was 34 in each group. Four out of five patients were white (15 [79%] in the retarded group and 16 [84%] in the control group).

Only 12 of the 30 possible life events actually occurred in the month before admission. Forty-six of the events were cited by both judges as relevant to 13 (68%) of the control patients and 11 (57%) of the retarded patients. The 19 retarded patients experienced 16 events; the control patients, 30. Although control patients averaged almost twice as many events as the retarded patients (1.5 versus 0.8), the difference was not statistically significant because of the small sample size.

The nature of life events differed for the two groups. Control patients were significantly more likely to exhibit changes in personal health habits, including eating and alcohol or drug use ($\chi^2=5.73$, df=1, $p<.01$). Most events for control subjects—20 (67%)—were habit changes, but these constituted only 19% (N=3) of the changes in the lives of retarded patients. Eight (50%) of the life changes for the retarded patients consisted instead of interpersonal conflict, compared with five (17%) of the events listed for control patients. Other changes noted more frequently for the retarded patients were separation from a significant other or residence change (three of the retarded patients versus one of the control patients). Jail or legal problems were noted for four of the control subjects but only one retarded patient.

Consistent with the relative predominance of interpersonal conflict over health and habit change in the lives of the retarded patients, on admission they evidenced more person-oriented physical aggression ($t=-1.81$, df=36, $p<.05$) and fewer intrapsychic problems ($t=3.05$, df=36. $p<.01$). Only seven (37%) of the retarded patients presented with an intrapsychic disturbance, compared with 17 (89%) of the control subjects. Only five (26%)—one in four—of the control patients had shown self-destructive or aggressive behaviors in the month before admission, but 11 (58%)—more than half—of the retarded patients had done so.

As to patients' final diagnoses, it is interesting to note that seven (37%) of the patients who were considered mentally retarded by the admissions service were not so diagnosed when they left the hospital, perhaps due to clinicians' focus on psychiatric problems during hospitalization. However, retardation was diagnosed subsequently in four of the five patients who used follow-up services. Other diagnoses applied were schizophrenia (N=3) and alcohol-related, personality, and other nonpsychotic disorders (N=1 each); one diagnosis was deferred. Patients in the control group were significantly more likely to have one of the affective or alcohol-related disorders than were the retarded patients ($\chi^2=16.69$, df=8, $p<.05$). Ten (53%) of the control patients were so diagnosed (five in each category), compared with only one alcohol-related disorder and no affective disorders diagnosed among the retarded patients. The groups did not differ in ratings of psychosocial stressors affecting them in the year before diagnosis (axis IV of *DSM-III*), but the retarded patients' mean axis V level of adaptive functioning at discharge (5.2, poor) was significantly worse than that of the control patients (4.2, fair) ($F=7.01$, df=1, 21, $p<.05$).

In regard to patients' use of the hospital, no differences between groups were observed in lengths of stay after the target admissions or in the number of hospitalizations in the years preceding and following the target episode.

DISCUSSION

These data suggest that admissions of retarded persons are precipitated more by the type of life changes (predominantly outward events involving conflicts or losses) than by their number, although a nonsignificant trend toward more events was observed for the group. Support was shown for our second hypothesis, that

mentally handicapped persons with psychiatric disorder are less likely to reveal typical intrapsychic symptoms and signs such as depression, worry, or changes in eating and sleeping patterns.

As expected, aggressive and self-destructive behaviors were more common among the mentally handicapped than among the other patients in the month before hospitalization. The contribution of the home environment to these behaviors is unknown. Perhaps caretakers tend not to notice intrapsychic indicators (including changes in eating and sleeping patterns) due to the "overshadowing" phenomenon. It seems important to determine whether the observed interpersonal conflicts follow early warning signs of intrapsychic stress. If so, caretakers could be trained to avert the escalated aggression that may lead to hospitalization.

Clinicians, too, need to learn to recognize symptoms of mental disorders as exhibited by mentally handicapped patients. In this study, intrapsychic problems were more difficult to discern when accompanied by mental retardation. Although the prevalence of affective illness among mentally and psychiatrically handicapped patients has been well documented (6–8), no retarded patient in this study was so diagnosed. In addition, the episodic use of the *DSM-III* 317–319 diagnoses, which hinders research into the special treatment needs of this group, may reflect both uncertainty about diagnosing this special population and failure to adequately consider their disability during treatment and discharge planning.

Although only 1% of the patients served by this facility were mentally and psychiatrically handicapped, the percentage is likely to increase over the next few years as deinstitutionalization continues. A major practical implication of this study is for clinical training programs to teach trainees to recognize, diagnose, and treat mental disorders in retarded individuals.

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Emergence of Depressive Symptoms in Patients Receiving Alprazolam for Panic Disorder

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The authors relate their clinical experience with 46 panic disorder patients who were receiving 3–10 mg/day of alprazolam. Fifteen (33%) developed symptoms consistent with DSM-III *criteria for major depression despite remission of their panic symptoms. Clinicians should be alert to this potentially reversible complication.*

(Am J Psychiatry 1987; 144:664–665)

Alprazolam is a triazolobenzodiazepine that is effective in treating generalized anxiety disorder (1); preliminary evidence suggests that it is also effective for panic disorder (2). We have observed the emergence of a major depressive episode in 15 (33%) of 46 patients with panic disorder who were treated with moderate to high doses of alprazolam in our anxiety disorders program. To our knowledge, this complication of alprazolam treatment for panic disorder has not previously been reported. The patients, all of whom met *DSM-III* criteria for agoraphobia with panic attacks or panic disorder, participated in an 8-week double-blind, placebo-controlled study. After 8 weeks the patients who had initially received alprazolam continued to receive it and those who had initially received placebo were treated with alprazolam for up to 1 year in a nonblind extension. No patient met criteria for major depression before the onset of panic disorder, and none of those who developed major depression according to *DSM-III* criteria after the onset of panic disorder were depressed at the time they entered the study. The following case reports illustrate the emergence of depressive symptoms in these patients.

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Supported in part by a grant from the Upjohn Corporation, Kalamazoo, Mich.

The authors acknowledge the assistance of Robin Dean and Beverly Brady in data collection and Vicki Brumbelow, Annette Spivey, and Alyce Ladd in preparation of the manuscript.

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CASE REPORTS

Case 1. Ms. A, a 32-year-old married woman, entered our anxiety disorders program with an 11-year history of agoraphobia with panic attacks. She had a history of major depression several years after the onset of her panic disorder but had no depressive symptoms at the beginning of treatment. Because she was adopted, a family history was unavailable. After an 8-week placebo treatment with no response, she received alprazolam in doses up to 5 mg/day. Her response was rapid and complete. She felt "normal for the first time in 11 years." However, after another 4 weeks, despite sustained remission of her anxiety symptoms, she developed depressed mood, anhedonia, anorexia with a 6-lb. weight loss over 2 weeks, psychomotor retardation, suicidal ideation, difficulty in concentration, and spontaneous crying spells. Sedation was present but readily distinguishable from the psychomotor retardation. At week 5 of alprazolam treatment, imipramine was added. Ms. A responded to 225 mg/day of imipramine over the next 4 weeks. She remained euthymic and panic free for the next 8 months while taking both alprazolam and imipramine.

Case 2. Mr. B, a 31-year-old hospital administrator, had a 10-year history of panic attacks with agoraphobic avoidance when he enrolled in our anxiety disorders program. He had no family history of depression or anxiety, and his past psychiatric history was negative. After a 6-week treatment with placebo, to which he did not respond, he was treated with alprazolam, up to 6.5 mg/day. He responded over the next 5 weeks with a cessation of panic attacks and a

substantial decrease in avoidant behavior. After 6 weeks at this dose of alprazolam, he developed depressed mood, anhedonia, anorexia, weight loss, loss of interest, decreased libido, and impaired concentration. Imipramine, 150 mg/day, was added to his regimen, and over the next 6 weeks his depressive symptoms abated. He remained stable, taking 4.5 mg/day of alprazolam and 150 mg/day of imipramine for the next 6 months, after which alprazolam was gradually discontinued without recurrence of symptoms.

These case reports typify the clinical course of 15 of 46 patients in our study who became depressed while receiving alprazolam. The maximum daily doses of alprazolam given to these 15 patients ranged from 3 to 10 mg/day (mean=6.6 mg/day), and the duration of drug administration ranged from 4 to 40 weeks. We could discern no differences in the psychiatric or family histories between the patients who experienced depression and those who did not. All of the patients who became depressed developed symptoms similar to those we have described, and all responded to treatment with imipramine or, in the case of one patient, desipramine.

DISCUSSION

We are not aware of any previous reports of depression complicating the treatment of panic disorder with alprazolam. This phenomenon has not been observed by other investigators participating in the multicenter study, although we have spoken with clinicians who have observed depression during alprazolam treatment. We are puzzled by the appearance of depressive symptoms in a substantial proportion of our sample of alprazolam-treated patients, especially in light of the antidepressant properties of this drug (3, 4). In fact, a report by Lesser and Rubin (5) indicated that alprazolam reduces depressive symptoms in patients who have agoraphobia with panic attacks. However, it should be noted that not all studies of the antidepressant efficacy of alprazolam have been positive (6, 7). Depression was cited as a reason for dropouts in a study of alprazolam in generalized anxiety disorder patients (1), but "depression" was poorly defined in that study.

It is not surprising that some of our patients developed depressive symptoms, since the occurrence of major depression in this population is common. Up to two-thirds of patients with panic disorder experience major depression during their lifetime (8). Also, benzodiazepines (in particular, diazepam) have been associated with the emergence or worsening of depressive symptoms (9). Interestingly, depression has recently been reported in patients undergoing long-term clonazepam treatment of panic disorder (10). The two most logical explanations for our observations are that alprazolam failed to prevent the emergence of spontaneous depression or that the drug contributed to the development of depression in these patients. We cannot say which is the correct explanation. Also, because most of our observations were made during open alprazolam treatment, they may have been influenced by rater bias.

The implications of our findings are of considerable interest on theoretical as well as clinical grounds. However, the primary purpose of this report is to highlight the clinical concerns that they raise. Our findings suggest that patients who receive high doses of alprazolam for panic disorder may develop secondary depression even when they become free of panic symptoms. Clinicians should be alert to this possibility, so that appropriate adjunctive treatment may be instituted in a timely fashion. Patients should also be made aware of the need to inform the treating clinician if they experience depressive symptoms. Although we cannot make definitive recommendations, our experience suggests that lowering the dose of alprazolam and rapidly instituting antidepressant treatment will usually be followed by resolution of depressive symptoms in these patients. We hope this report will stimulate further study of this clinical problem.

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Relationship Between Physical Anomalies and Age at Onset of Schizophrenia

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Among 50 schizophrenic patients grouped by age at onset, the group with onset at or before age 18 had significantly more subjects with minor physical anomalies. These findings suggest that early-onset schizophrenia is associated with a more compromised CNS.

(Am J Psychiatry 1987; 144:666–667)

In at least certain subgroups of schizophrenic patients the disorder appears to be associated with cerebral dysfunction (1). In addition, and possibly related to the dysfunction, schizophrenic patients have shown an increased prevalence of minor physical anomalies (2), which are associated with insult to the fetus during the first trimester of pregnancy. These anomalies, including curved fingers, furrowed tongue, and low-seated ears, could be due to genetic as well as a variety of teratogenic factors. Similar increases in such anomalies have been noted among autistic (3) and schizophrenic (2) children, but to our knowledge the relationship between the presence of such anomalies and the time of onset of schizophrenic symptoms has not been addressed. Although *DSM-III* does not distinguish between those with early and late onset, there is evidence suggesting a difference. For example, Kolvin (4) found that, unlike an adult-onset group, an early-onset group included a preponderance of males (5:2), a delay in speech development, and more evidence of cerebral dysfunction. In addition, Fish (5) reported many signs of cerebral insult among schizophrenic children.

Given the evidence of increased cerebral insult among patients with an early onset, it seems worthwhile to consider other potential correlates of early onset. In particular, physical anomalies may be more prevalent among those with an early onset of symptoms than among those whose symptoms emerged later in life.

Received Aug. 4, 1986; revised Dec. 23, 1986; accepted Jan. 29, 1987. From the UCLA Research Center, Camarillo State Hospital. Address reprint requests to Dr. Green, UCLA Research Center, Camarillo State Hospital, Box A, Camarillo, CA 93011.

Supported in part by a grant to Dr. Satz from the Scottish Rite Foundation.

The authors thank Donna Gaier and Nita Mize for their assistance in the preparation of this report.

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METHOD

The subjects were 50 (42 men, 8 women) Caucasian inpatients from Camarillo State Hospital, Camarillo, Calif. Each subject received a *DSM-III* diagnosis of schizophrenia based on an expanded version of the Present State Examination (6). The sample was divided into three groups on the basis of age at first institutionalization according to medical records or, when such information was unavailable, the patient's recollection of onset (N=2). On the basis of two peaks at 18 and 21 years, we defined the groups as follows: early onset=age 18 or earlier (N=20), middle onset=age 19–21 years (N=16), and late onset=age 22 or later (N=14). The three groups did not differ in medication level (in chlorpromazine equivalents), but age at the time of the study was significantly different between the early- and late-onset groups (mean±SD=29.5±8.3 versus 35.4±7.0 years, respectively; $t=2.17$, $df=32$, $p<.05$). There was also a significant difference in years of education between the early- and middle-onset groups (mean±SD=9.9±3.3 versus 11.9±1.6; $t=2.26$, $df=31$, $p<.05$).

After the procedures were fully explained and informed consent was obtained, a slightly modified version of the Waldrop Scale (7) for assessment of physical anomalies was administered. We did not include the measurements for head circumference and epicanthal distance because we are establishing our own norms. The Waldrop Scale requires a 5–10-minute examination and assesses anomalous features of the hair, ears, eyes, mouth, hands, and feet. The raters were blind to the subjects' age at onset. The scale used was basically the same as that used previously with schizophrenic adults (2).

RESULTS

There was no difference in the mean number of anomalies between the men and women (mean±

TABLE 1. Relationship Between Age at Onset of Schizophrenia and Physical Anomaly Score

		<3 Anomalies		≥3 Anomalies	
Time of Onset	N	N	%	N	%
Early (≤18 years)	20	10	50	10	50[a]
Middle (19–21 years)	16	15	94	1	6
Late (≥22 years)	14	13	93	1	7

[a]Significantly higher than for middle-onset group (p=.005) or late-onset group (p=.009) (Fisher's exact test).

SD=1.55±1.50 versus 1.50±1.31, respectively). Consequently, sex was not considered in the subsequent analyses. A subject was designated as having significant anomalies if he or she received a score of 3 or higher. The cutoff score of 3 was chosen because our pilot data indicated that this was the upper limit for a normal population. A Fisher exact probability was calculated for the number of subjects in each onset group who exceeded the cutoff score. The results, listed in table 1, show that the early-onset group had a significantly higher percentage of subjects above the cutoff than either the middle-onset (p=.005) or late-onset (p=.009) group. When the middle- and late-onset groups were combined, the relationship was strengthened (p=.0001). There was no difference between the middle- and late-onset groups. The most common anomalies were high-steepled palate, tongue with smooth-rough spots, and large gap between the first and second toes (N=10 for each).

DISCUSSION

These data suggest that indicators of first trimester insult are found disproportionately among early-onset schizophrenic patients. The middle- and late-onset groups did not differ in rate of physical anomalies from our pilot control group. While preliminary, the results suggest that during the prenatal period such patients may have sustained CNS injury that placed them at risk for an early onset of schizophrenia. Conversely, early-onset schizophrenia may be associated with a CNS that is more labile and susceptible to prenatal injury. Regardless, the results indicate that early- and adult-onset schizophrenia may represent different etiological subtypes.

Reviewing the literature on birth complications and schizophrenia, McNeil and Kaij (8) concluded that schizophrenic patients show a higher prevalence of obstetrical complications than normal control subjects. McNeil and Kaij also reported that, among schizophrenic patients, those with obstetrical complications tended to have first received psychiatric treatment at an earlier age. This is consistent with our findings because factors leading to obstetrical complications may also result in minor physical anomalies.

Guy et al. (2) cited an unpublished study by Goldfarb and Botstein in which there was a high rate of minor anomalies among schizophrenic children, although they were not compared with adult patients. In our study the early-onset group primarily experienced onset during adolescence; thus it is difficult to compare the findings to those of patients with childhood onset.

Our results, while preliminary, indicate that schizophrenic patients with an early onset have significantly more minor physical anomalies than groups with later onsets. The anomalies could be due to genetic or teratogenic factors. The results are consistent with the theory that early-onset schizophrenia involves a more compromised CNS and may constitute a separate subgroup. This theory is being evaluated further by administering measures of laterality and information processing to the different onset groups.

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Sleep EEG Findings in Depressed Children and Adolescents

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Sleep polysomnographic data on 17 juveniles (age 9 to 14) with major depression revealed abnormalities similar to those in depressed adults.
(Am J Psychiatry 1987; 144:668–670)

Four polysomnographic abnormalities are found in adults with endogenous depression: 1) sleep continuity disturbances, 2) reduced delta (slow wave) sleep, 3) increased eye movement density during the early REM periods of the night, and 4) shortened REM latency (1, 2). In some adults (3) these abnormalities may persist with clinical remission.

To our knowledge, three polysomnographic studies of depressed children and adolescents are available. Puig-Antich et al. (4) found that symptomatic depressed children did not differ polysomnographically on any sleep EEG variables from age-matched normal subjects or from nondepressed children. Young et al. (5) found no polysomnographic variable that discriminated depressed patients from age-matched normal subjects. However, Lahmeyer et al. (6) found significantly shorter REM latency and greater REM density in 13 depressed adolescents than in 13 age-matched normal subjects. A negative correlation between REM latency and age was also found, a finding supported by the normative sleep studies by Coble et al. (7) of 100 children age 6–16 years. These reports suggest that pubertal status affects the likelihood of shortened REM latency occurring in depressed patients.

Different criteria for designating sleep and REM onset may contribute to variations among studies. For example, Kupfer's group requires a minimum of 3 minutes to designate the onset of REM sleep. In this laboratory, about 10% of first REM periods were shorter than 3 minutes in normal adults.

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The authors thank India Davidson for her secretarial support.
Supported in part by grant MH-39188 from NIMH and by the Biological Humanics Foundation.

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METHOD

The sample consisted of 17 juvenile inpatients (age 9–14 years) with major depression, 13 of whom were melancholic according to *DSM-III*. There were 11 boys and six girls. Their mean±SD age was 12.3±1.5 years. Ten patients were prepubertal (stages 1–3) and seven were postpubertal (stages 4 and 5) (8). The mean±SD ages for the pre- and postpubertal subgroups were 11.9±1.8 and 12.9±0.7 years, respectively, and were not significantly different. Informed consent was obtained from the parents and assent from the subjects.

The evaluation included physical/neurological examinations and routine laboratory tests, including thyroid function tests. Each patient and both parents were independently assessed with a semistructured psychiatric interview by two of us (G.J.E. and W.A.W.), who then independently completed the Bellevue Index of Depression (9). The mean±SD Bellevue depression score for the group was 70.2±6.8 (range=58.5–82.5); a score over 20 is consistent with depression (9). Within 2 weeks of admission the Diagnostic Inventory for Children and Adolescents (10) was completed with the child and parents separately. The two independent semistructured and structured interview results were reviewed, and a consensus diagnosis was made.

Three consecutive nights of polysomnographic recordings were conducted after at least 14 drug-free days, with methods and scoring criteria that have been previously described (2, 3). Sleep onset and REM latency were also calculated with criteria developed by Kupfer et al. (1) and employed by Coble et al. (7): sleep onset is the beginning of the first 10 minutes of sleep that contains no more than 2 minutes of stage 1 non-REM sleep, waking, or movement artifact; the first REM period must be at least 3 minutes in duration. Our scoring of REM latency has no "3-minute rule." Attempts were made to keep the total sleep time equal to the times that were routine for the child before the recordings by using sleep logs for the 5 days before the laboratory recordings and a sleep history. Only the data from nights 2 and 3 were used to calculate the mean values we compared. When the night 3 value was not available (N=4), the night 2 value alone was used to compute the mean.

TABLE 1. Polysomnographic Variables of 10 Children With Major Depression and 27 Normal Control Subjects[a] Age 12 or 13 years

Sleep Variable[b]	Depressed Children		Control Subjects		Significance	
	Mean	SD	Mean	SD	t (df=35)	p
Total recording period (minutes)	499.9	23.5	478.3	40.0	2.01	<.05
Time spent asleep (minutes)	463.4	33.2	451.1	37.6	0.96	<.2
Sleep efficiency (time asleep/total recording period×100)	92.0	4.9	94.4	1.6	1.52	<.1
Terminal time (minutes)	0	0	1.1	3.3	—	—
Awake time (%)	2.5	1.6	1.2	—	—	—
Number of arousals	13.4	5.6	2.5	2.1	6.00	<.001
Sleep latency (minutes)	25.7	21.9	20.3	6.0	0.77	<.2
Stage 1 (%)	5.8	3.1	8.1	3.7	1.90	<.1
Stage 2 (%)	48.7	7.0	50.5	3.9	0.77	<.2
Stage 3 (%)	8.6	3.8	8.3	2.2	0.24	<.2
Stage 4 (%)	11.0	6.0	12.6	4.2	0.78	<.2
REM latency minus awake time (minutes)	90.0	29.7	119.3	27.9	2.71	<.01
REM time (minutes)	109.4	25.6	91.3	16.8	2.07	<.05
REM activity (units)	316.0	94.6	110.7	50.1	6.53	<.001
REM density (REM activity/time)	2.9	0.73	1.17	0.42	6.95	<.001
Number of REM periods	4.9	0.6	4.1	0.7	3.43	<.001
First REM period						
REM time (minutes)	14.0	4.6	12.6	6.6	0.72	<.2
REM activity (units)	30.4	12.2	9.2	7.1	5.17	<.001
REM density	2.07	0.40	0.67	0.30	10.07	<.001
Second REM period						
REM time (minutes)	21.7	7.6	26.2	10.0	1.87	<.05
REM activity (units)	51.4	18.2	31.3	23.0	2.77	<.02
REM density	2.53	0.49	1.09	0.44	8.15	<.001

[a]Data from study by Coble et al. (7).
[b]Average of nights 2 and 3.

RESULTS

No significant difference between the pre- and postpubertal groups on any sleep EEG measure was found. When the REM latency scoring was based on the "3-minute rule," 17% (eight of 47) of the patient-nights reflected an unusually long REM latency, which was, in fact, the time to the *second* REM period of the night. The different scoring of sleep onset had virtually no effect on the REM latency scoring. The considerable differences in the REM latency means and standard deviations between our scoring and the Kupfer method (76.8±19.1 versus 88.6±26.3 minutes) resulted almost entirely from the effects of applying the "3-minute rule."

Lacking our own control group, we compared the data from patients of age 12 or 13 years (N=10) to published data on normal control subjects age 12 or 13 years (N=27) (7) based on the same scoring system (see table 1). Significant differences were found with t tests in number of arousals, REM latency, REM activity, REM density, and number of REM periods. With the Bonferroni correction, an acceptable level of significance would be p<.0025.

DISCUSSION

These results agree with those of Lahmeyer et al. (6). Our pubertal depressed subjects had a shorter REM latency than normal subjects. Contrary to prevailing beliefs, both prepubertal and postpubertal depressed juveniles evidenced sleep architecture changes similar to those in depressed adults, which is consistent with the finding of Coble et al. (7) that pubertal status has little impact on sleep measures. Although the same scoring method was used for REM latency in our study and theirs, we scored REM activity units on a 0–4 scale in 30-second epochs, which is similar to but not exactly the same as scoring 1-minute epochs on a 0–8 scale, as Coble et al. did. However, the REM density figures suggest more REM activity in our sample than in theirs. For example, during the first REM period in the 12- and 13-year-olds they studied, in any minute the average number of eye movements was fewer than one, whereas our sample had an average of more than two eye movements per minute.

Some differences may exist between the sleep of depressed juveniles and adults (e.g., fewer sleep onset difficulties). The presence or absence of puberty per se, however, does not protect depressed children from having a shortened REM latency and other sleep architecture differences. These findings suggest that the polysomnographic data from depressed juveniles may provide valuable physiological information pertinent to depression.

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Early Identification of Renal Problems in Patients Receiving Chronic Lithium Treatment

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Serum β_2-microglobulin and creatinine values were compared with creatinine clearance in 20 lithium-treated patients. β_2-microglobulin, but not creatinine, correlated significantly with creatinine clearance, indicating that β_2-microglobulin is a more sensitive test than serum creatinine for monitoring glomerular filtration rate in chronic lithium therapy.
(Am J Psychiatry 1987; 144:670–672)

The effects of chronic lithium therapy on kidney function have been widely reported (1). Most studies support the fact that lithium induces a defect in urinary-concentrating ability (2), but the effect of lithium on glomerular function remains controversial (3). A number of studies, however, have shown that prolonged treatment with lithium may result in a diminution of glomerular function (4), as measured by changes in glomerular filtration rate.

Most clinics monitor glomerular filtration rate in patients receiving chronic lithium therapy by measuring serum creatinine and, occasionally, by determining creatinine clearance. It has been shown that serum creatinine is not an adequate marker of glomerular filtration rate, particularly in glomerular diseases (5). Therefore, attempts have been made to select a more suitable test to measure more accurately variation in glomerular function. Wibell (6) showed that serum β_2-microglobulin can be used effectively for detection of even a slight decrease in glomerular filtration rate. In a prospective study of insulin-dependent diabetic patients, Viberti et al. (7) reported that β_2-microglobulin concentration detects early reduction of glomerular filtration rate better than serum creatinine concentration does.

The purpose of this study was to confirm the correlation between serum level of β_2-microglobulin and creatinine clearance and to compare the usefulness of β_2-microglobulin with serum creatinine in the monitoring of glomerular function in a group of patients receiving chronic lithium therapy.

METHOD

The sample consisted of 20 patients, 12 women and eight men, receiving chronic lithium therapy who gave full consent to participate in this study. Ages ranged between 33 and 70 years (mean=52 years). Three patients had received lithium for between 6 months and a year, seven for 1–5 years, and 10 for more than 5 years. Daily doses of lithium varied from 900 to 1,800 mg.

Received March 13, 1986; revised Dec. 5, 1986; accepted Jan. 29, 1987. From the Departments of Medicine and Psychiatry, the New York Hospital-Cornell Medical Center. Address reprint requests to Dr. Samiy, the New York Hospital-Cornell Medical Center, Westchester Division, 21 Bloomingdale Rd., White Plains, NY 10605.
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TABLE 1. Serum Creatinine and β_2-Microglobulin Levels and Creatinine Clearance in 20 Patients Receiving Long-Term Lithium Therapy

Patient	Age (years)	Lithium Therapy (years)	Creatinine (mg/dl)	β_2-Microglobulin (mg/liter)	Creatinine Clearance (ml/min/1.73 m^2 body surface area)
1	68	5	1.3	4.40	50.3
2	68	11	1.3	2.70	71.9
3	58	9	1.1	3.40	61.0
4	59	9	0.8	3.20	62.3
5	62	8	2.3	6.90	27.4
6	58	9	0.9	2.80	72.6
7	64	11	1.3	8.00	40.5
8	68	11	0.9	4.30	64.9
9	49	1	1.1	2.70	102.5
10	47	2	1.7	2.80	72.9
11	33	2	0.8	1.90	126.9
12	40	5	1.2	2.40	148.0
13	70	0.5	1.0	3.00	51.0
14	46	12	1.2	2.20	117.5
15	33	3	1.1	2.10	90.1
16	33	1	0.9	3.10	75.6
17	36	2	0.9	1.90	105.6
18	53	10	0.9	4.20	77.9
19	54	9	0.7	5.40	86.9
20	42	4	0.9	1.00	90.3

The blood sample for assay of β_2-microglobulin, creatinine, and lithium was taken when patients were in the fasting state in the morning after a 24-hour urine collection. Serum β_2-microglobulin value was measured by radioimmunoassay (8), creatinine concentration in the serum and urine was measured by the Fabiny technique (9), and serum lithium was measured by flame photometry.

Correlations among creatinine, creatinine clearance, and β_2-microglobulin values were computed by the Pearson product-moment method for both the raw data and logarithmic transformation. Log transformations were performed before parametric analyses to normalize the distribution of scores.

RESULTS

As shown in table 1, serum β_2-microglobulin levels ranged from 1.00 to 8.00 mg/liter (normal range=0.54–2.75 mg/liter), the range of serum creatinine levels was 0.7–2.3 mg/dl (normal range=0.5–1.2 mg/dl), and creatinine clearance ranged from 27.4 to 148.0 ml/minute per 1.73 m^2 body surface area (normal range=70–157 ml/minute per 1.73 m^2). Twelve patients (60%) had elevated β_2-microglobulin levels. Fifteen patients (75%) had normal levels of serum creatinine, four patients (20%) had slightly elevated levels, and one had an elevated creatinine level. Thirteen patients had creatinine clearance in the normal range, and seven patients (35%) had reduced creatinine clearance.

Among the 12 patients with elevated levels of β_2-microglobulin, all but three had a below-normal creatinine clearance. Except for one, all of the 10 patients with a low creatinine clearance had elevated levels of serum β_2-microglobulin. Of 19 patients with normal or slightly elevated serum creatinine values, seven (37%) had below-normal creatinine clearance. The one patient with a high serum creatinine level (2.3 mg/dl) had a marked reduction in creatinine clearance (27.4 ml/minute per 1.73 m^2) and an elevated level of serum β_2-microglobulin (6.90 mg/liter). Of the four patients with a slightly elevated or upper-normal level of creatinine (1.3–1.7 mg/dl), two had below-normal creatinine clearance and three had above-normal β_2-microglobulin levels. The correlation between log creatinine clearance and log β_2-microglobulin was significant ($r=.71$, $p<.05$).

Eight of the 10 patients (80%) treated with lithium for more than 5 years had elevated serum β_2-microglobulin values and decreased creatinine clearance. In contrast, only two of the 10 patients who had been taking lithium for 1–5 years had elevated levels of serum β_2-microglobulin. Most of the patients (five of six) over 60 years old had a low creatinine clearance and an elevated serum β_2-microglobulin value.

DISCUSSION

The results of our study show that there is a significant correlation between serum levels of β_2-microglobulin and creatinine clearance. By contrast, there was not a significant correlation between serum creatinine level and creatinine clearance. Only in three patients with marked elevation of β_2-microglobulin values and below-normal creatinine clearance was there an elevated level of serum creatinine. Four of seven patients with low creatinine clearance would have been missed if the only test we had used had been serum creatinine level. Similarly, eight of 11 patients with elevated levels of serum β_2-microglobulin showed

normal serum creatinine values and might not have been identified as having impaired renal function.

For three cases in our data, the creatinine clearance was normal and the serum β_2-microglobulin level was high. This discrepancy may have resulted from inaccurate 24-hour urine collection, a problem common with the creatinine clearance test.

In summary, our study confirms the finding of Viberti et al. (10) that serum β_2-microglobulin level shows an early reduction of glomerular filtration rate better than serum concentrations of creatinine. In extending this work to patients receiving chronic lithium therapy, we found that the level of β_2-microglobulin, in contrast to that of serum creatinine, was always elevated when creatinine clearance was below 70 ml/minute per 1.73 m^2. In our study, if serum creatinine level had been the only test to detect renal damage, eight of 11 patients with low creatinine clearance would have been overlooked. In conclusion, we recommend that despite the higher cost, the measurement of serum β_2-microglobulin, instead of serum creatinine, be used for periodic monitoring of glomerular filtration rate in psychiatric patients receiving chronic lithium therapy.

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American Board of Psychiatry and Neurology Examination Application Deadline

Applications for the 1988 part I examination are currently being accepted by the ABPN. All applications must be received in the Board's executive office no later than September 1, 1987. No application requests will be taken after August 28, 1987. The tentative date for the 1988 part I examination is April 12, 1988. Address correspondence to Stephen C. Scheiber, M.D., Executive Secretary, ABPN, One American Plaza, Suite 808, Evanston, IL 60201.

ECG Changes During Haloperidol and Pimozide Treatment of Tourette's Disorder

George Fulop, M.D., Robert A. Phillips, M.D., Ph.D., Arthur K. Shapiro, M.D., J. Anthony Gomes, M.D., Elaine Shapiro, Ph.D., and Johanna W. Nordlie, M.A.

The ECG QTc interval was significantly prolonged by pimozide but not haloperidol or placebo in a randomized clinical trial with 40 patients with Tourette's disorder. However, no adverse cardiac effects or differences in rate, rhythm, or waveform were found.

(Am J Psychiatry 1987; 144:673–675)

Pimozide, a diphenylbutylpiperidine, is the only alternative to haloperidol approved by the Food and Drug Administration (FDA) for the treatment of Tourette's disorder (*Physician's Desk Reference,* 40th ed., p. 1091). However, ECG abnormalities found in 10% of patients treated with pimozide prompted the FDA to advise "periodic" ECGs (*PDR* and 1). The ECG abnormalities found include T wave and U wave abnormalities and prolongation of the QTc interval (the time during which the heart contracts and relaxes). Prolongation of the QTc interval increases the risk of a potentially fatal arrhythmia, such as torsade de pointes (2). Cardiac arrhythmia was suspected as the cause of the sudden deaths of two schizophrenic patients during acute titration of pimozide to 70–80 mg/day in 2 weeks (3). In this study we examined the ECG changes during treatment of Tourette's disorder patients with haloperidol, pimozide, and placebo and assessed the utility of ECG monitoring at 3-week intervals while adjusting dose.

METHOD

The subjects were 32 males and 10 females; their mean±SD age was 21±11 years (median=18, range=18–47). They were independently diagnosed by two clinicians as fulfilling the *DSM-III* criteria for Tourette's disorder. They participated in a 21-week randomized, double-blind, crossover study comparing haloperidol, pimozide, and placebo. All patients or their parents signed informed consent forms for participation in the study. No patient who had a QTc interval, with Bazett correction (4), greater than 0.44 seconds or concurrent physical illness was included. Previous medications, if any, were discontinued before entry into the study. Each subject received a baseline standard 12-lead ECG followed by 3 weeks of placebo treatment.

Each treatment segment lasted 6 weeks. After the 3-week placebo phase, each patient was randomly assigned to one of four different clinical tracks: 1) haloperidol-pimozide (12 weeks), 2) pimozide-haloperidol (12 weeks), 3) placebo-haloperidol-pimozide (18 weeks), and 4) placebo-pimozide-haloperidol (18 weeks). The double crossover study design allowed for pooling of data if there were insufficient data for any one track. Two patients (one in each of tracks 3 and 4) declined to complete the final treatment segment, resulting in a final sample of 40 patients.

The patients were given strict dosage schedules that were designed to have the dose reach the maximum allowed by the sixth week. However, the dose was individually titrated during each treatment segment to achieve optimal clinical response—maximum benefit, i.e., percentage of tic reduction (1), with minimum adverse effects. The maximum dose was 10 mg/day (0.15 mg/kg per day) of haloperidol and 20 mg/day (0.3 mg/kg per day) of pimozide. Benztropine mesylate was administered for extrapyramidal or akinesic adverse effects.

ECGs were obtained at baseline and at 3-week intervals within each treatment segment (midpoint and endpoint) and were blindly rated by a cardiologist (R.A.P.) for rate, rhythm, electrical interval, and waveform abnormalities (flat, notched, biphasic, or inverted T waves or U waves greater than 25% of T wave height).

Statistical significance for all continuous variables was assessed by means of repeated measures analysis of variance (ANOVA) and covariance with pairwise contrasts adjusted by the Bonferroni method. For dichotomous items the binomial test was used as a

Presented at the 139th annual meeting of the American Psychiatric Association, Washington, D.C., May 10–16, 1986. Received April 28, 1986; revised Dec. 12, 1986; accepted Jan. 29, 1987. From the Department of Psychiatry, the Department of Electrocardiography, the Department of Medicine, Division of Cardiology, and the Tourette and Tic Laboratory and Clinic, Mount Sinai School of Medicine. Address reprint requests to Dr. Fulop, Box 1229, Mount Sinai Hospital, 1 Gustave L. Levy Place, New York, NY 10029.

Supported by grant NS-20529 from the National Institute of Neurological and Communicative Disorders and Stroke.

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small sample alternative to McNemar's test (5). All correlations presented are Pearson product-moment correlations.

RESULTS

The mean±SD dose at the haloperidol endpoint was 4.6±2.8 mg/day (range=0–10), or 0.054±0.04 mg/kg per day (range=0–0.15). For pimozide it was 7.5±5.9 mg/day (range=0–20), or 0.093±0.096 mg/kg per day (range=0–0.3). The mean ratio of pimozide to haloperidol endpoint dose was 1.6:1, slightly less than the 2–3:1 ratio reported by Shapiro and Shapiro (1). The mean daily dose of benztropine mesylate at endpoint was not different for haloperidol (0.34±0.91 mg/kg) and pimozide (0.41±0.93 mg/kg) (two-tailed paired t test, t=−1.28, df=39, p=.21).

There were no significant changes in any of the ECG variables during placebo treatment for the 13 patients who received placebo for a total of 9 weeks. These patients did not differ from those who received placebo for only 3 weeks in baseline characteristics of Tourette's disorder, ECG variables, or endpoint medication doses. Therefore, the ECG findings of these 13 patients were combined with those of the patients who received placebo for only 3 weeks, resulting in two tracks—placebo followed by 1) haloperidol-pimozide or 2) pimozide-haloperidol.

Repeated measures analysis of variance, using the haloperidol and pimozide endpoint ECG variables as the dependent variables and subject, period, sequence, and treatment as the independent variables, revealed no significant period or sequence effects (p>.26 in all cases). Similarly, no significant carry-over effects were found for Tourette Severity Scale score (1) or percentage of tic reduction (1), which may affect the selection of optimal dose and in turn affect ECG characteristics. Furthermore, no significant Pearson correlations were found between dose and ECG variables after haloperidol and pimozide treatment or between dose and severity of Tourette's disorder or percentage of tic improvement at endpoint. Therefore, the analyses of treatment effects were completed with the repeated measures ANOVA without period and sequence effects or with the binomial test for discrete data.

No difference was noted between mean±SD heart rate at baseline (69±12 beats/minute, range=49–91) and at haloperidol endpoint (69±12, range=48–94) or pimozide endpoint (70±10, range=55–94) (repeated measures ANOVA, F=0.69, df=2, 78, n.s.). There was also no difference for rhythm or for the QRS interval (baseline=0.085±0.001 seconds). One patient had a slight increase in notching of T waves while taking pimozide, and another patient manifested a flattening of T waves while taking haloperidol. No patients had abnormal U waves or inverted T waves.

The mean±SD QTc interval was significantly higher at pimozide endpoint (0.404±0.030 seconds, range=0.354–0.456) but not at haloperidol endpoint (0.388±0.028, range=0.322–0.459) than at baseline (0.384±0.022, range=0.329–0.429) (repeated measures ANOVA, F=12.15, df=2, 78, p<.0001). The mean±SD difference between the baseline and endpoint QTc intervals was significant for pimozide (19.0±4.0 seconds; t=4.65, df=39, p<.0001) but not for haloperidol (4.1±3.8 seconds; t=1.07, df=39, n.s.) (pairwise contrasts). No difference was found between the midpoint (3 weeks) and endpoint (6 weeks) QTc intervals for haloperidol (t=0.84, df=39, n.s.) or pimozide (t=0.14, df=39, n.s.) (paired t tests). QTc intervals longer than 0.44 seconds developed in two patients while they were taking both active medications, six while they were receiving pimozide, and only one who was taking haloperidol (binomial test, N=7, X=1, p=.12). Repeated measures analyses of covariance for age, sex, and previous medication did not reveal any significant effects on the QTc interval besides the main effect of pimozide. The Pearson product-moment correlation was not significant for endpoint dose of benztropine mesylate or active medication, age, heart rate, or QRS and QTC intervals.

DISCUSSION

To our knowledge, this is the first study of ECG changes during treatment of Tourette's disorder with haloperidol, pimozide, or placebo. No adverse clinical cardiac effects or syncope occurred during treatment. Although the QTc interval was significantly prolonged by pimozide, this change was not clinically meaningful. Although more patients taking pimozide than haloperidol had QTc intervals greater than 0.44 seconds, the accepted clinical criterion for normal (2), the difference was not statistically or clinically significant.

The differential effect on the QTc interval may be related to the fact that pimozide and other diphenylbutylpiperidines have calcium-channel-blocking properties but butyrophenones do not (6). Impeding the influx of calcium delays cardiac repolarization, thereby increasing the QTc interval detected on the ECG.

In view of the overall effectiveness and safety of pimozide, periodic ECGs may be unnecessary in patients without histories of cardiac disease or prolonged QTc intervals. These results are limited to situations involving dose titration by 0.5 mg every two days and a maximum dose of 0.3 mg/kg per day, or 20 mg/day. One must acknowledge, however, that the absence of adverse clinical effects may be the result of an inadequate sample size (type II error); therefore, replication of the study data is necessary.

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Deceased Members of the American Psychiatric Association

The deaths of these members were reported to APA between Dec. 11, 1986, and Feb. 25, 1987.

James Allen Abbott
Klaus Angel
Herbert Barry, Jr.
William C. Battle
Lauretta Bender
Jean-Helios M. Bermingham
Roger Biron
Charles J.G. Blackford
Bernard M. Blum
Bruce Buchenholz
Dean P. Carron
Abraham H. Center
Remo R. Cerulli
Charles E. Comfort
Harry Costeff
William Cybuch
Lee Andrew Dean
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Paul L. Dunstan
Eric Jordan Ekstedt
Frank G. Engler
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Louis Goldstein
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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

PSYCHOANALYSIS

Freud: Appraisals and Reappraisals, *edited by Paul E. Stepansky. Hillsdale, N.J., Analytic Press, 1986, 267 pp., $24.95.*

Once the private domain of psychoanalysts, studies of Freud are now in open season, with hunters coming from many disciplines. This onslaught or renaissance reflects recent exploration of the unrestricted archives. This first volume in a series entitled Contributions to Freud Studies brings together original works of Freudophiles of differing backgrounds and viewpoints. These include three major essays—one by Peter Swales, a Rolling Stones aide turned *enfant terrible* of the Freud archives; Edwin Wallace IV, M.D., a psychiatrist and historian of medicine; and Barry Silverstein, M.A., a professor of developmental psychology. Adding brief contributions on this safari are Patrick Mahony, Ph.D., a professor of English and Canadian analyst; Paul Stepansky, Ph.D., editor of the series and biographer of Freud's circle; and the psychoanalyst John Gedo, M.D.

Swales seems to enjoy the role of master poacher on the Freud preserve. His "Freud, His Teacher, and the Birth of Psychoanalysis" is worth the price of the book. With ever-ingenious archival discoveries he unmasks the "Frau Cäcilie M." of Breuer and Freud's *Studies on Hysteria* (1) as Anna von Lieben, a wealthy Viennese hostess and poetess. Although hers was—probably for reasons of confidentiality—a fragmentary case report in the *Studies,* Swales says Freud called her his "teacher" in arguing that this Anna was Freud's Anna O., a (or the) seminal case in the development of psychoanalysis. Swales succeeds convincingly in elaborating the case history, complete with substance abuse, pathological identifications, a family history of psychiatric illness, and intriguing hypotheses about patient and therapist motivations. Moreover, he beautifully recreates the milieu in which Freud and his patients lived and worked, offering dozens of interesting historical revisions and speculations. There are provocative discussions of hypnosis, opiates, and the evolution of Freud's thought and technique.

Swales writes in a cheerfully chatty tone that can be both engaging and irritating. It is as if a gossip were confiding delicious secrets, pausing over jokes, asides, and enchanting details that help to bring the story to life. His flourishes and sensuality of style evoke nineteenth-century Vienna. Swales's pride in his own clever detective work intrudes, however: footnotes at times become flamboyant defenses of his misadventures with other Freud hunters. Even if the style and the author's claims may be slightly overblown, this is important and stimulating work.

Dr. Wallace follows with "Freud as Ethicist," a generally clearsighted if somewhat familiar survey of Freud's complex and even contradictory moral stance. Although Freud did not consider himself an ethicist, Wallace feels that he has had more impact on ethics and morality "than perhaps any individual since Christ or Paul" (p. 84). In briefly covering a potpourri of difficult issues, Wallace comments on the conflict between repressive morality and impulse in pathogenesis, the inevitable tension between individual instincts and society's need for their restraint, determinism and free will, and Freud's attitude toward religion. Readers of Rieff (2) may not find much new, and the text reads slowly after the pyrotechnics of Swales, but this is a nice overview of Freud's ethical and moral positions.

Professor Silverstein's " 'Now Comes a Sad Story': Freud's Lost Metapsychological Papers" is an interesting look at Freud's plan to publish 12 essays during World War I. Of these, five reached print, including "Instincts and Their Vicissitudes" (3), "The Unconscious" (4), and "Mourning and Melancholia" (5). Silverstein uses the lost seven essays as an opportunity to explore the vicissitudes of the antebellum psychoanalytic circle, especially Freud's response to the apostasies of Adler and Jung and his desire for apotheosis in psychoanalysis. This is the sort of "psychohistory" wherein motivations may appear almost too straightforward, but the author provides good documentation, writes gracefully, and makes a nice case for the influence of Freud's ambitions and conflicts on his published and unpublished work.

As for the brief contributions, Mahony's piece on "The Oral Tradition, Freud, and Psychoanalytic Writing" provides a curious shift by focusing on the role of sound and voice in psychoanalysis. He says little about what is traditionally termed oral tradition, however, and comes close to caricaturing his point with an exaggerated and exclamatory emphasis on sound and audition. Readers may be bemused to hear that they live in the Era of Second Orality (p. 200). Stepansky's "Feuerbach and Jung as Religious Critics" neatly contrasts two very different approaches to religion, a difference of some moment because of Freud's reliance on Feuerbach. John Gedo's "On the Origins of the Theban Plague" is a charming essay whose points are not obscured by its strained neo-Sophoclean subtitles. Gedo notes that Freud has become a culture hero. If in the past psychoanalysts writing on Freud tended to distort him through idealization, other writers today bring their own transferences to Freud, sometimes failing to see him in proper historical context. Gedo's interest in the motivations and projections of Freudographers provides a fitting close to the volume.

Essay collections suffer from eclecticism. This is the case but also the ostensible point of this volume. Yet, ironically, there is less heterogeneity than might be expected. The authors focus more on Freud's historical context than on his metapsychology. And if the stated purpose of this book is to bring together disparate viewpoints, this seems largely a *fait accompli.* At least three of the contributors belong to the Section on Psychiatric History at Cornell University Medical College in New York, and they frequently cite one another. The reader is left with the sense that the authors share an interdisciplinary awareness if they do not always agree.

Clearly printed in a comfortably large typeface, the book suffers from occasional typographical errors. If it doesn't always capture big game, it is well worth owning as a

secondary text and overview of contemporary Freudiana. It seems to be aimed at a general psychologically minded audience as much as psychoanalysts.

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Narcissism, the Self, and Society, *by Reuben Fine. New York, Columbia University Press, 1986, 343 pp., $35.00.*

This book is an effort to integrate the recent developments in psychoanalysis with its history. Fine focuses on the concepts of "self" and "narcissism." He presents an erudite history of the use of the terms by historians, philosophers, and psychologists. There seems to be a stress on examples of pathological narcissism rather than the healthy narcissism present in all of us. Fine then reviews the history of psychoanalytic theory, emphasizing his view that Freud's theory was understandable until 1905, when the focus was on libido (love), and that Freud erred after 1914, when under the impetus of anger at Jung's defection and the need to encompass narcissistic neuroses, he unnecessarily confused his theory by introducing the concepts that led to the structural theory and the emphasis on aggression. Fine believes that the 1905 theory with a few updates would provide "a comprehensive modern theory of psychoanalysis without the tortured and convoluted theories of the later metapsychology" (p. 67).

Summarizing the status of the concept of self, Fine delineates three contemporary theories: the Freudian self (a common-sense use of the term, as in discourse), the social self (the self as viewed by culturalists), and the Kohutian self (a superordinate entity guiding the individual's destiny throughout life).

The remainder of the book presents the social-psychiatric and culturalist view of the formation of the self. Anthropological studies demonstrate that personalities in each culture vary tangibly from one another and demonstrate the impact of the idiosyncratic culture on the individual raised in that culture. The evidence is presented in the context of an enormous bibliography. There is no doubt that cultural and group influences help shape the psyche of the individual. Should one, however, view psychoanalysis as the study of complex psychological states and see the self as an independent center of initiative, then one would engage the clinical point of view and learn to recognize and foster the subtle life-sustaining narcissistic transferences that are present in most psychoanalyses and most psychotherapies.

There are other interesting threads that run through the book: the unusual emphasis on the period of psychoanalytic theory before 1905, when the libido (love) theory was dominant as being ideal; the classification of cultures into love cultures and hate cultures, with most cultures disappointingly being hate cultures; and the focus on the repetitive striving in the human race to establish a Utopia. There seems to be a motive to find an ideal state or circumstance.

This book is recommended to those interested in a display of erudition and to those with a culturalist-anthropological accent in their theoretical orientation.

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Psychoanalysis: Freud's Cognitive Psychology, *by Matthew Hugh Erdelyi. New York, W.H. Freeman and Co., 1985, 287 pp., $24.95; $14.95 (paper).*

Although Freud succeeded in transforming the twentieth century's image of human nature and, at the same time, had a profound effect on the practice of all psychotherapy, academic psychology has been relatively skeptical of his contributions. The great merit of *Psychoanalysis: Freud's Cognitive Psychology* is that it attempts to find common ground between experimental psychology and psychoanalysis in order to re-awaken that tradition which has long sought to integrate both schools of thought.

Erdelyi is surely correct in thinking that psychoanalysis does not deserve to survive as an independent, dissociated entity, incapable of being challenged by the normal canons of psychological evidence. At the same time, he is also bold, given the usual state of academic opposition to psychodynamic thinking, in insisting that formal psychology, as taught in universities, requires the enrichment that can come from the psychoanalytic perspective.

Although this book serves as an absolutely excellent introduction for students, specialists can find faults with it. From a clinical point of view the citations to the post-Freudian literature will doubtless seem unnecessarily sparse; the author makes no mention, for example, of any work by figures like Bruno Bettelheim, Erik H. Erikson, or Erich Fromm, not to mention writings by so-called deviants like Otto Rank. And the historian will be surprised by many striking bibliographical omissions; it is a bit odd to read a detailed account of Freud's discussion of the "aliquis" parapraxis without being told that it has been established as an autobiographical exploration on Freud's part. Nonetheless, the strength of *Freud's Cognitive Psychology* lies in the comprehensive scope with which it addresses its objective; it has chapters covering psychoanalytic psychotherapy, the unconscious, models of the mind, twilight phenomena, and defense processes.

Freud was of course the greatest writer in the school of thought he founded, and therefore it makes good sense to use his formulations as the main bridge to academic psychology. Yet one hopes the time will come when it will also be possible, without any disrespect to Freud's historic achievement, for university psychologists to be equally at home with the thinking of those who have done their best to update his findings. Clinical experience as well as social and political changes since the turn of the century have led to legitimate revisionist efforts within psychoanalysis that ought to be of significance to academic psychology.

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Freud and the Imaginative World, *by Harry Trosman, M.D. Hillsdale, N.J., Analytic Press, 1985, 224 pp., $24.95.*

Harry Trosman has addressed an interesting aspect of Freud's relation to the development of ideas in a compact, well-written, neatly ordered book. Fortified by access to Freud's personal library, Trosman brings new knowledge regarding "Freud's link with the humanities . . . [and how] literary models guided his pen" (p. xi).

The book is of interest to those who struggle to understand the epistemological significance of the Freudian corpus and those who are interested in great men. The chapters "Freud and the Formative Culture" and "Modes of Influence on Freud's Creativity" are jewels in the study of a creative individual.

Although there is much to disagree with in Trosman's study of the role of influence on creativity, the data that he presents are impressive. Yet, I feel he does not enough distinguish between *being* influenced and *feeling* influenced. The criterion for creativity is the emergence of something new that is related to the past and portends for the future, not something that arises *de novo*. In this respect an analogy can be drawn to the day residue and the dream, an idea Trosman advances but does not develop. The day residue often organizes the dream, anchoring it to the ongoing. Similarly, in creativity, events including specific intellectual influences can be seen as organizers. Viewed this way, intellectual influences, even the commission (defined broadly or narrowly), become part of the creative process. Such a view moves away from the rigorous dichotomy between influence and originality that Trosman struggles with. In this regard, Trosman does himself a disservice by referring repeatedly to the "neurotic symptom *or* the dream" (emphasis added). Although there are many psychodynamic similarities between the neurotic symptom and the dream, there are remarkable differences. Had Trosman emphasized the differences between dreams and neurotic symptoms, he would have found, as Freud did, that the dream provides many useful analogies for understanding creativity.

Trosman's second area of discussion, a section entitled Psychoanalysis and the Arts, accurately emphasizes the differences between aesthetic pleasure and conflict resolution. In "The Psychoanalysis of Aesthetic Response," Trosman uses the structural theory to great advantage, giving strong emphasis to ego functioning and ego gratifications in creativity. I think that, had he remained with literary criticism rather than approaching "the arts," this would have been a stronger section. Yet, Trosman makes an important contribution by emphasizing the psychoanalytic study of the creative product in its own right.

Trosman adds little by restudying the controversy over Freud's Leonardo monograph (1), although it is helpful to have the controversy succinctly presented and well documented and to have Walter Prater brought to the attention of psychoanalysts. Likewise, the study of Hamlet is thin, even though it is interesting to see how Trosman understands the dynamic tension in the play. I think Trosman does himself and psychoanalysis a disfavor by joining the currently fashionable trend within and without psychoanalysis to discredit the position that artistic creativity is personally revealing. This trend, I feel, is a reaction to the poor psychoanalytic scholarship that has led to ridiculous isomorphic formulations linking events in creative persons' lives to their work rather than a legitimate reaction to weaknesses in the paradigm.

I was sorry to see Trosman repeat the overquoted 1946 aside of Lewin that applied psychoanalysis has "become a parlor game for analysts, a means for discharging clinical frustrations or unresolved conflict by working with patients who cannot talk back" (p. 183). The fact is that those who work in this field *suffer* from the frustration of not having a subject who can answer a question, let alone talk back, and the lack of criteria for confirmation.

I am sure Trosman is aware of the limitations in his final chapter "Psychoanalytic Views of Creativity." Yet, it is of interest to have a well-reasoned study of "an adaptive ego whose function it is to produce an object that is imaginatively new, communicable, and socially valued" (p. 201). I am not sure that we would want to use "socially valued" as a criterion for creativity unless we had an extraordinary historical perspective on what is considered socially valuable. Trosman's study is further limited by bowing too strongly toward "innate disposition" (p. 204). Freud had the hubris to study the irrational (the dream and neurotic symptoms) rationally. Although Freud demurred from this path with regard to creativity, I think we should follow his overall commitment to positivism and not this specific bypass. Further, Trosman, by giving little emphasis to developmental considerations, deprives himself of acknowledging the beginnings psychoanalysis has made in understanding creativity developmentally.

Trosman's references are a model of breadth, accuracy, and erudition even though there is a shortage of developmental studies. It is my view that had the book been limited to the literary influences on Freud, his mode of thought, and his style of writing and the effect of Freud on literary thinking and style, the book would have been outstanding.

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Forty-Two Lives in Treatment: A Study of Psychoanalysis and Psychotherapy, *edited by Robert S. Wallerstein. New York, Guilford Press, 1986, 784 pp., $45.00.*

This enormous book is written by a very distinguished traditional psychoanalyst with the highest credentials, a matter of great importance in reviewing this book because, although many investigators were involved in gathering and organizing some of the data and establishing a consensus about the patients and their treatment, the book consists essentially of formulations, summaries, and discussions that ultimately represent Wallerstein's personal opinions. It presents the stories of 42 individuals who were treated in the Psychotherapy Research Project of the Menninger Foundation and their follow-up over a period of 30 years. Half were treated in "psychoanalysis" and the other half in "equally long-term expressive and supportive psychoanalytic psychotherapies" (p. vii). Special emphasis is placed on illuminating the "mechanisms" of supportive psychotherapy. The author had an important role in the project over several years, and the 42 case summaries were "constructed" by him (p. 9).

The book, a combination of research data and anecdotal case material with theoretical discussion, is divided into nine

major sections and five appendixes. The first section describes the study and illustrates the enormous complexities and problems involved in trying such a project; it summarizes as well other publications that arose out of the project, also by formidable authors. The second section describes the methods and design of the study in detail. Experts in research design will have much to say about this, but it is valuable as a starting point for discussions of how to design a study of psychoanalysis and psychotherapy that can be labeled "research" in a way that will satisfy the criteria used in "normal" science, if one thinks this is worthwhile to do.

The third section describes the patients, but—deliberately (pp. 34–35)—no updating to *DSM-III* is given, a fact that will annoy a number of psychiatrists. The table of patients presented on pages 180–181 will not only annoy but enrage some psychiatrists, especially those interested in feminist issues—for example, the designations "Bitter Spinster" and "Involutional Woman," among others, detract from the serious intent of the work.

The fourth section, which is long and valuable, describes in detail the types of treatment used and what factors the author feels to have been significant in effecting changes in the treatment planning. It should be kept in mind that the patients were not a representative outpatient sample but from the Menninger Clinic; many of these patients were away from their home settings, and some were hospitalized. We also discover that the author, as promised on page 28, refers to patients by their designated epithets, such as "Snake Phobia Woman" or "Divorced Nurse," a style that I found most disconcerting and may also be problematic for some other readers; one cannot help speculating what this implies about the ambience of the project as a whole.

The next two sections, about 250 pages, represent the heart of the book. Section five presents the cases of patients in "psychoanalysis and expressive psychotherapy," and section six presents those in "expressive-supportive psychotherapy." Wallerstein uses an anecdotal style to summarize treatment descriptions, present formulations involving complex dynamics (often prefaced with the word "clearly"), and provide a theoretical discussion and opinions. For example, the following themes of a patient ("Phobic Woman") are presented from her analysis: "It became clear that her fear of a more active sexual life was based on the oedipal meaning of the marital relationship, with the simultaneous fear of the father's angry retaliation if she truly tried to establish a mature sexual life with the husband" (p. 274). One either accepts or rejects the many, many formulations of this nature on the basis of trust in the author's judgment and report of the consensus of the investigators—take it or leave it. On the foundation of such judgments, theoretical discussions of various aspects of therapy are entered into and more judgments are made about what went wrong when it did and why. For example, on pages 319–320 a list of conclusions is offered about the limitations of the treatment of one patient, followed by the statement, "It has been abundantly clear . . . that there was also an internal push from within the patient toward particular outcome limitations" (p. 320). The author goes on to carefully explain this in deep psychodynamic terminology, and I am not quarreling with his formulation, since it is "abundantly clear," but the matter stands or falls on whether the reader trusts that if something is abundantly clear to Dr. Wallerstein, that is sufficient.

Rather parenthetically, before his description on page 322 of the patient called "The Prince," Wallerstein notes that the formulations of narcissistic patients were made before those in Kohut's publications. He briefly refers to his own views of self psychology and his effort in previous publications to eschew the new theoretical structure of self psychology, since he believes that "the psychiatric states underlying the selfobject transferences [and countertransferences] are themselves but variant expressions of intrapsychic conflict and can take their place within, and as part of, the mainstream of psychoanalytic [conflict] theory" (p. 322). To say the least, this is a controversial point of view.

The great emphasis of the book is on "expressive-supportive psychotherapy" and how it works; discussions of this topic are scattered throughout (e.g., pp. 389, 451, 689, and elsewhere). We begin to understand the main thesis of the book as it moves into section seven, with anecdotal and statistical reports of the outcomes of the treatments, and section eight, with similar reports of the follow-ups. What the investigators learned, we are told in the final section, is that patients treated with psychoanalysis and expressive psychotherapy did not do as well as expected and patients treated with expressive-supportive psychotherapy did better than expected. This, the author points out, is partly a function of the patient population available at the Menninger Clinic for psychoanalysis, who tended to be more sick than most patients in private practice and therefore, in the author's opinion, required modification with "supportive parameters" (p. 729). The final conclusions are summarized on page 730; these fit Wallerstein's earlier contention that "the blurring of the interface zone between psychoanalysis and intensive psychoanalytic psychotherapy did indeed emerge in our findings" (p. 687), as did "a similar blurring of the interface between the expressive and the supportive therapeutic modes" (p. 687). These conclusions are based on the presence of major supportive elements in all the psychotherapies. The author hopes that this will enhance the "conceptual dignity to be accorded the supportive psychotherapeutic mode, psychoanalytically formulated" (p. 734).

Wallerstein has attempted an enormous task, presenting a vast amount of clinical and research material and supplementing it with theoretical discussions of many aspects of psychotherapy and psychoanalysis. It is doubtful that anyone could have done a much better job, although it is possible to quarrel with some of the organization of the material. For example, I found it difficult to skip back and forth quickly from case descriptions to discussion of general theoretical problems and would have preferred more separation of these. Also, better summaries at the end of each chapter would have enabled one to pick and choose more effectively which chapters would be of the most interest, since so many kinds of approaches—from descriptive and statistical tables to deep psychoanalytic formulations—are packed into this book.

I left the hardest question for the end of this review. Who will want to read this book? I don't think it will satisfy anybody. Research experts will attack the design, psychiatrists will object to the nomenclature, psychoanalysts will argue over the formulations and theoretical statements, lawyers will question the ethics of the whole report, feminists will decry some of the epithets and treatment statements, behaviorists will contest the formulations of the "mechanisms" of supportive psychotherapy it offers, and biological psychiatrists will sneer at the whole thing. Therein lies also the strength of the book: it contains something to provoke everyone into thinking and arguing, and it serves excellently as a baseline for further attempts at research and at better delineation among the psychotherapies, between supportive and expressive psychotherapy, and between intensive psy-

chotherapy and psychoanalysis. For those psychiatrists with plenty of time and a skeptical mind, Wallerstein's prodigious effort will stimulate a lot of rethinking and a review of one's basic assumptions in clinical work.

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FORENSIC ISSUES

Psychiatry, Human Rights and the Law, *edited by Martin Roth and Robert Bluglass. New York, Cambridge University Press, 1985, 241 pp., $47.50.*

"Doctor knows best" is a major theme of this collection of 16 papers from a 1983 conference on psychiatric-legal issues. Today, several of the authors lament, the psychiatrist finds his or her authority undercut by challenges from civil libertarians, lawyers, former patients, homeopaths, chiropractors, cultists, and even from "consumerism." At the same time, society expects the psychiatrist to take on the burden of its most troublesome misfits. "One must sympathize," writes Robert Campbell, the director of a private psychiatric hospital in Manhattan, "with the psychiatrist pressured to control, ameliorate, or abolish nonconformity by a society that files complaints against him for doing its bidding."

The largest number of chapters review recent (1983) and not-so-recent (1959) changes in civil commitment statutes in the United Kingdom. Changes in legal standards for hospitalization in Italy, Germany, Canada, and the United States are the subject of one chapter each. These chapters are not likely to find a large audience because they tell more than most readers will want to know about statutory details but less than readers need to know about the application of the laws. In the United Kingdom, for example, statutes enacted in 1959 and 1983 enlarged patients' rights to challenge involuntary commitment, at least on paper. Did these changes—rather small steps by American standards—make a practical difference? Or were they mere ripples on a larger tide? One must look elsewhere (for example, reference 1) for the answers.

Potentially, the most important of these chapters is the one by P. Sarteschi, G.B. Cassano, M. Mauri, and A. Petracca on Italy's Psychiatric Care Act of 1978. Italy has mandated a truly radical reform: the abolition of public mental hospitals and their replacement by outpatient treatment and voluntary treatment in general hospitals. Sarteschi et al. claim that partial implementation of the statute has produced "an absolutely chaotic situation." Among other effects, they say, the new law has "completely disoriented physicians and psychiatrists." Unfortunately, the authors have not backed up their polemic conclusions with substantial citations, examples, details, or data—a limitation their chapter shares with most, although not all, of the others. Significantly, the authors do not cite Mosher's study, published in this *Journal* (2), which was based on 7 months of research in Italy and reached diametrically opposite conclusions. Mosher stated that Italy's revolutionary turnabout in mental health law and practice did not spring from Utopian visions of ex-patients but from years of effort by Franco Basaglia, the director of a large state mental hospital.

Other chapters deal with the insanity defense in the United Kingdom (Nigel Walker) and in Denmark (Villars Lunn); with psychopathy and dangerousness (William H. Reid) and dangerousness in social perspective (Jean Floud); and with the organization of psychiatric services in British prisons (John Gunn and John R. Hamilton). The best of these is Gunn's chapter on the role of psychiatry in the penal system. His chapter is one of the briefest, only 10 pages long, and is refreshingly free of the sententious and seemingly ex cathedra pronouncements that burden much of the book. Gunn is dissatisfied with what he sees as fragmentation, waste, and misuse of psychiatric resources. His complaints are familiar and plausible. If his fellow authors wrote as clearly as he, one could anticipate solutions with more optimism.

This collection of conference papers leaves one with the dominant impression of familiar opinions restated but not reinforced by new data. Too often, the conclusions seem self-evident. For example, 30 pages into a 59-page chapter, Margaret Somerville concludes, "Changes in the circumstances in which values must be evaluated . . . alter the decision outcome."

During 1981–1984 many articles on the subjects covered in this 1985 book appeared in this *Journal* (references 3–6, for example), but none of them is cited. Most readers with limited time will find those articles, and other articles and books (references 7 and 8, for example), a more rewarding source of information on the important topics of psychiatry's interface with law and human rights.

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Psychiatry, Law and Ethics, *edited by A. Carmi, S. Schneider, and A. Hefez. New York, Springer-Verlag, 1986, 315 pp., $71.20 (paper).*

The Washington Hilton hosts many professional meetings, and many of those attending have exited from the lower-level side entrance to T Street, walking over the spot where John Hinckley shot President Reagan. The Hinckley case refocused attention on psychiatry, law, and ethics, and much work remains to be done where these areas meet.

The volume under review consists of 58 chapters representing talks given at a conference in Israel. The chief editor is identified as Judge Amnon Carmi, who edited or co-edited four previous volumes in Springer-Verlag's Medicolegal Library. Each selection in this volume is very short and often

reads like a transcribed talk. The variety of topics is huge, with no unifying theme, ranging from abortion in female adolescents under German law to such new disciplines as "normatology" and "human structurology." Many chapters will have limited appeal to American audiences: the three articles on commitment of mental patients in Israel, the one on commitment in Japan, and one on how the insanity defense works in Nigeria. The book contains more than the usual number of errors of grammar, style, and proofreading.

J.R. Rappeport discusses whether psychiatrists paid to testify in court should reveal everything. Unfortunately, it is difficult to discover his views. "Indexing Civil Commitment Criteria in Psychiatric Emergency Rooms" by S.P. Segal, M.A. Watson, and L.S. Nelson is an excellent article. These authors present a careful study of how emergency room physicians rate the dangerousness of patients when deciding whether they should be involuntarily admitted. They have developed a testing instrument called TRIAD that measures clinicians' judgments about dangerousness; this instrument might be useful in applying legal criteria uniformly and consistently.

There are several articles on ethical issues, ranging from the anecdotal to vague ramblings. Generally, discussions of medical ethics are best when subjected to the constraints of an actual case. One article started off in this way with the Phillip Becker case (the teenager with Down's syndrome whose parents declined to give consent for his cardiac surgery). Author S.S. Herr gives in to passionate indignation and castigates the parents. He draws parallels between the Becker case and the Baby Doe case in Indiana, blasting the Indiana Supreme Court and the U.S. Supreme Court and stating that a mass murderer would receive more due process than Baby Doe (p. 236). Herr fails to point out that the issue before the courts was whether parental decisions in such cases should be overturned, forcing parents of children with Down's syndrome, for example, who never leave home and live on their own to spend 30 or more years caring for a child against their will. Self-righteous, simplistic moralism such as Herr's does nothing to help us in such agonizing cases. Indeed, such responses are part of the problem. In a similar vein, N.S. Lehrman, in "The Prostitution of Psychiatry: The 1930s in Germany and the 1980s in America," accuses modern American psychiatry of preparing the way for another Nazi era. He concludes, "In America also, psychiatry has been performing some of the functions of an Inquisition: injuring innocents, both patients and dissenters, and exculpating criminals, terrorists especially" (p. 46).

The majority of the chapters directly or indirectly concern psychiatrists, psychiatric social workers, and other therapists and their relation with Israeli law (one of the editors, Professor Schneider, is based in a school of social work in Israel). The title is slightly misleading in that only 20 pages directly concern ethical issues, even though such issues inevitably weave through the entire book.

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A Clinician's Guide to Forensic Psychological Assessment, *by Michael P. Maloney. New York, Free Press (Macmillan), 1985, 214 pp., $22.95.*

Michael Maloney is a psychologist at the University of Southern California (USC) School of Medicine who also does consultant work. He credits his interest in the field of "forensic psychology" to the late Seymour Pollock, M.D., a colleague of many of us, who directed the program in psychiatry and law at the USC School of Medicine. As in the remainder of the mental health field, the boundaries between forensic psychology and forensic psychiatry are blurred. Hence, although much of what Dr. Maloney says could just as well be said about forensic psychiatry, he has in some ways attempted to make his book a practical guide to forensic psychological assessment and to offer it to mental health professionals. In this he would have succeeded if the word "introductory" were added to the title. At times there is an absence of enough specifics or advice—an eternal hope in this adversarial arena. Since Dr. Maloney defines forensic psychology as being composed of two major parts, psycholegal research and expert witness testimony, the overlap with forensic psychiatry is very large.

What about the content of the work? It would be adequate as an introduction to the main topics. Parts seem quite cogent, such as that dealing with psychological assessment for workers' compensation and personal injury evaluations, but others remain sketchy and need supplementation. There are good illustrations of written reports of many cases, yet the firsthand feel of court testimony and the adversarial qualities this brings to the fore as well as a definition of how the reports will be used if the ultimate test should arise in a courtroom are lacking.

The perspective taken in the book is that although the legal system is often adversarial in reaching decisions, the legal and mental health professions do not need to be so. Given the nature of the judicial system and the inherent conflict that gives rise to legal cases, this may be a fond hope and often doomed to failure. Traditional topics are covered, such as insanity, evaluation of sex offenders (co-authored), assessment of violence potential, personal injury evaluation, malingering, and child custody. A final chapter dealing with expert testimony is only 10 pages long and would not suffice even for a beginner. Dr. Maloney has wisely written separate chapters dealing with different aspects of competency, such as competency to stand trial, competency in civil matters, and competency to waive *Miranda* rights and make confessions. Often these various areas of competency are fused and treated in discussions as though they are generic. Dr. Maloney, referring to psychologists, states that during their graduate training they "have had little or no experience with the application of psychological principles to the legal system. Much of the difficulty with psychological testing and/or assessment is due to poorly trained or incompetent examiners"; we could surely agree with his stricture with respect to psychiatric training. When we then add on top of this an adversarial legal system that is often seeking to contradict testimony, we have a setting of different professions attempting to apply mixed concepts with different standards and ideas about the need or desirability for such participation.

Where I think Dr. Maloney waxes more optimistic than may be warranted is in his position that "psychological research can make a potentially great contribution." He believes that with additional funding for more, such research will have an increasing impact on the legal system. Even if more funds were forthcoming for such a purpose (itself highly dubious), the areas he believes will yield conclusions that will be "readily accepted" by the legal system have already been fairly well researched. He refers to malingering, assessment of the potential for violence, and the developmental ability to appreciate a *Miranda* warning. It is not that more knowledge would be undesirable, but it would be contrary to the nature of the judicial system to be looking for

research results from the psychological or psychiatric fields to settle matters. The discoveries of psychology and psychiatry are as fraught with contrary opinions as is the legal system. Whatever the empirical claims of psychology or psychiatry and whatever the inferences made on the basis of these claims can lead only to the opposing side's attempting to rebut them. The "hard facts" in a courtroom are never truly "hard"—a jolting reminder to our humbleness when we wander into areas outside our customary familiarity.

The type of book Dr. Maloney has written is becoming increasingly popular. We can expect more such volumes to be published. It serves introductory needs but would require supplementation in a course. However, for the psychiatrist who does any type of patient or consultant work or who uses human subjects for research, it is a concise formulation of the issues that should begin to be in their awareness.

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CHILD PSYCHIATRY

The Effects of Autism on the Family, *edited by Eric Schopler and Gary B. Mesibov. New York, Plenum, 1984, 353 pp., $35.00.*

Autistic Children: A Guide for Parents and Professionals, *by Lorna Wing, M.D. New York, Brunner/Mazel, 1985, 174 pp., $19.50.*

Infantile autism was defined as a syndrome as recently as 1943 by the late Dr. Leo Kanner of John Hopkins School of Medicine. Early theories stressed psychogenic etiologies and viewed parents as contributors to the child's psychopathology. Research over the past decades has exonerated parents. A major shift toward neurological hypotheses has occurred, and biological research into etiology and treatment is flourishing.

Although this disorder remains poorly understood, this shift, in conjunction with other forces, has resulted in changing attitudes of professionals toward parents. Rather than prescribing psychotherapy for parents as contributors to their child's problems, we now try to engage parents as therapists and advocates for their children. Parents and professionals now collaborate in treatment and in obtaining appropriate community resources for autistic children. This change has resulted in efforts to investigate the impact of the presence of an autistic child on families, both parents and siblings. Although considerable progress has been made in defining effective treatments for autistic children, the best treatments currently available do not effect cures, and prognosis generally remains poor. This state of affairs requires that professionals dealing with autistic children attend to the needs of families who are stressed by the presence of an autistic child, adolescent, or adult.

The two books reviewed here reflect these changes. The first examines the effects of autism on the family, outlining changes in professionals' attitudes toward parents and in parents' roles as advocates and therapists for their children and as teachers of professionals and other parents. This volume offers a compelling, in-depth look at the emotional impact of autism on families, with a good balance between empirical research and personal accounts of parents and siblings. One in a series of annual volumes on topics related to autism, this book should increase our awareness of the practical and emotional problems faced by families. It provides a helpful conceptualization of family needs, supplemented in many places with guidelines for meeting these needs. Early diagnosis, realistic prognosis, and a wide range of community resources are highlighted.

The editors introduce this volume with a progress report on the changing professional attitudes toward parents over the past 40 years, thus providing an important historical perspective on the following chapters. In the first chapter Edward Zigler discusses the history of social programs and treatment modalities, which too often have been based on unrealistic expectations and social fads. He discusses the two basic systems within which the child functions, the family and the treatment center or school; urges early intervention, continuity between interventions, and an increasing focus on social competence; and outlines social policy needs. Dennis Cantwell and Lorian Baker then review research negating the role of the family environment as an etiological agent and the limited research raising the possibility of genetic contributions. They also review research documenting the stress experienced by families and the effects of home-based therapy programs, pointing out the need for research on the effects of linguistic interactions on the course of autism. In the next chapter, the editors describe the TEACCH model, which encompasses a broad range of interdisciplinary services, parent-professional collaboration, advocacy, and community relations.

A section on parents as advocates includes a chapter on developmental changes experienced by families, written by a parent, Mary S. Akerley, who offers insights into the importance of early diagnosis and recognition of the problem, realistic expectations, and planning over the child's life span, including the point at which the child becomes an adult and leaves home. She acknowledges and discusses the importance of a healthy family life "beyond the child's handicap." Frank Warren provides a nice historical overview of the National Society for Children and Adults With Autism (NSAC), an organization that has been central in providing support to families. Siegfried Pueschel and James Bernier discuss the professional's advocacy role in securing appropriate services. James Surratt's chapter on advocacy discusses ways of effectively changing policies and systems that affect autistic children.

In the section entitled Parents as Trainees, David Kolko reviews preliminary data suggesting that parents can be effective behavior therapists for their autistic children while acknowledging the need for additional research on this approach. His chapter addresses problem areas such as failures to generalize to new settings and describes different behavioral techniques, parent training techniques, and program evaluation issues. Martin Kozloff's chapter addresses family needs beyond that of educating the child and describes a program designed to meet these broader needs. Parents are encouraged to select behavioral goals for the child on the basis of functionality and their cost/benefits within the family setting. Laura Schreibman and her colleagues review background research on parent training and describe their program as well as their research on program evaluation. They conclude that parent training is superior to clinic treatment but note some tendency for parents to prefer direct clinic treatment over parent training interventions. Sandra Harris and Michael Powers use a family systems framework to conceptualize the impact on a family of the child throughout the life cycle. To sensitize professionals to family experience, they discuss the developmental tasks the family faces at each stage. I think that the chapters which look beyond parent

training to broader family experiences and issues would be especially helpful to those involved with behaviorally based parent training programs.

The section entitled Parents as Teachers includes a chapter by Dr. Schopler and two chapters by parents who have dedicated their professional lives to developing services for autistic individuals. Dr. Schopler gives a thumbnail sketch of how parents have influenced his perceptions and approaches to treatment. Dr. Sullivan comments on her personal experiences with legislators, other parents, and researchers and urges parent involvement and collaboration in all sectors. Barbara Cutler describes her personal development from "helpless parent" to special education teacher and trainer of parents and professionals and notes the special contributions the parent-professional can make in terms of helping professionals to understand parents' perspectives.

The final section deals with emotional support for parents and siblings of autistic children. Victoria Shea's chapter, "Explaining Mental Retardation and Autism to Parents," provides clear guidelines for effective interpretive interviews with parents. Marie Bistol's chapter, "Family Resources and Successful Adaptation to Autistic Children," discusses stress and coping in families. She reviews research directed at identifying high-risk and protective factors for family adaptation. Of particular interest are two findings: 1) ambiguity with respect to the nature of the child's problem can have a more adverse effect on families than a clearly defined view of the handicap and 2) family stress may increase rather than decrease as autistic children get older. The author identifies helpful supports and coping strategies, again broadening avenues of intervention that might be used with the disorder. In "Coping With Burnout," Lee Marcus provides a conceptual model of burnout and analyzes factors leading to burnout in families as well as strategies for intervention. Untempered and unrealistic enthusiasm and neglect of one's personal needs are but two of these factors, which professionals working with families can help to address. "Children With Handicapped Brothers and Sisters" by Susan McHale and others examines the literature on siblings and concludes that effects on siblings are not unequivocally negative. They identify possible contributions to the different outcomes with a view toward future research needs. And, finally, Robert Fromberg provides a personal account of his experience with increasing responsibility over time for his younger brother, who was autistic, in "The Sibling's Changing Roles."

The strengths of this book for me were its combination of reports of empirical data and personal experiences and its broad focus on the families not merely as change agents for their autistic children but as units and individuals with their own needs. The stresses of having a handicapped child and their impact on the family may well be underestimated or neglected by professionals trained to diagnose and treat individual patients. Even those professionals who are accustomed to working with families may neglect family needs in the context of treatment programs set up to treat a disorder like autism. The current limitations for effecting a cure for autism and evidence that this handicap can take a heavy toll in terms of maternal depression and family stress certainly call for greater attention to helping families survive and thrive.

The second book, *Autistic Children: A Guide for Parents and Professionals* by Lorna Wing, is a guide for parents and perhaps for professionals without expertise in child psychiatry. It includes a great deal of basic information but does not cite research or report on it with any detail and thus appears intended for the layman. Part one, Description of the Children, contains definitions of autism, epidemiologic findings, descriptions of specific behaviors across the life span along with interpretations of such behaviors, theories of causation, and comparisons with other childhood disorders.

Part two, Education and Management, includes chapters on the roles that doctors, teachers, and parents can play in diagnosis and treatment. The section on parents' roles contains a long list of characteristic behavioral problems, with concrete descriptions and interventions that may be tried, including a brief description of basic operant principles. The strength of this section is the inclusion of many concrete examples of problems seen in autistic children and concrete suggestions for intervention. Successful implementation of behavioral intervention strategies might well require professional help in this difficult population, however. Also included in this second section are chapters on the family, various types of services for autistic children, the role of societies of parents, and outlook for the future, which includes prognosis, research, and education.

The strengths of this guide or manual are its practical approach, use of lay terminology and avoidance of technical jargon, and brevity. A list of books on autism is provided at the end for additional reference. Although this book provides a nontechnical introduction to autism, relatively sophisticated parents might well look to some of these additional readings for a more in-depth view of this poorly understood disorder.

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Early Identification of Children at Risk: An International Perspective, *edited by William K. Frankenburg, Robert N. Emde, and Joseph W. Sullivan. New York, Plenum, 1985, 393 pp., $42.50.*

The early detection of children at risk and the remediation of developmental problems have been an important focus of both research and service programs for many years; an initial emphasis on aspects of primary prevention has been expanded to include aspects of secondary and tertiary prevention as well. The increasing awareness of the complex problems involved in developing and evaluating screening and intervention programs has tempered early enthusiasm and, as exemplified by this volume, has given rise to more sophisticated and varied approaches. This volume, which results from the Fourth International Conference on Children at Risk, held in 1984, provides a current summary of work in early detection and screening of developmental problems. The 35 chapters present a range of viewpoints and approaches both interdisciplinary and international in scope. The chapters are grouped into sections reflecting the historical background of screening, the social environment of the child at risk, new approaches to screening, and regional and national programs for early identification.

The historical background provided helps to place subsequent sections within a broader context and will be particularly helpful to readers less familiar with basic concepts. Issues of sensitivity, specificity, and the problems of identification of the child at risk are summarized. The second section highlights new approaches to the assessment of affective, social, and environmental risk factors and has implications for a broadened understanding of the risk concept. The importance of interdisciplinary approaches to screening is highlighted by the descriptions of screening

programs for a variety of medical, behavioral, cognitive, communicative, and other problems. New experimental approaches, the availability of longitudinal and follow-up data, and an appreciation of methodological problems add considerably to the volume. The final section of the book is more distinctly international in tone; a series of generally brief chapters describe programs in developed and developing countries.

This volume reflects the diversity of existing approaches to detection and screening of children at risk for developmental disorders. This diversity is, potentially, a source of strength for the field; the methodological and theoretical issues highlighted in the book should help to facilitate research and service programs. Given the current state of knowledge and limitations imposed by space it is not surprising that some aspects of early detection, such as screening for psychiatric disorders in early childhood, social policy implications of early identification programs, and the implications of early detection for inappropriate "labeling," receive less attention. Indeed, a similar volume could be devoted to aspects of intervention. On the whole, however, the volume presents a current and valuable summary of the state of the field. As such, it is of greatest interest to pediatricians, child psychiatrists, psychologists, educators, and other professionals concerned with early detection and intervention programs.

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TEXTBOOKS

The Spectrum of Psychiatric Research, *edited by Michael Shepherd. New York, Cambridge University Press, 1984, 240 pp., $29.95.*

This volume is a compendium of 39 commissioned editorials published in *Psychological Medicine* since 1970. Each of the editorials is a brief critical review of the literature in an area of psychiatric research. Most of the contributors are from the United Kingdom, and most of the editorials were published in the mid- to late-1970s.

The overriding purpose of this volume, according to the editor, is to provide "authoritative reviews of the many branches of scientific inquiry that are related to psychiatry . . . neurobiological, psychosocial, and clinical sciences" (p. vii). Indeed, the scope of this volume is broad, with nine reviews from the neurosciences, four from genetics, five from psychopharmacology, seven from psychology, six from epidemiology, and eight from general psychopathology and clinical issues. The roster of contributors is also distinguished, including (to name but a few) B.E. Tomlinson ("Plaques, Tangles and Alzheimer's Disease"), J. Shields ("High Risk for Schizophrenia: Genetic Considerations"), H.J. Eysenck ("Psychological Theories and Behaviour Therapy"), J.H. Gruzelier ("Cerebral Laterality and Psychopathology: Fact and Fiction"), J.K. Wing ("Methodological Issues in Psychiatric Case Identification"), W.A. Lishman ("Research Into the Dementias"), and T.J. Crow ("The Scientific Status of Electro-Convulsive Therapy").

The major thrust of each of these editorials is to indicate areas in need of further elaboration and exploration, based on what has already been established. To use Professor Tomlinson's 1982 review of the status of neuropathology in Alzheimer's disease as an example, the relationship between plaques and tangles is unknown, and the role played by plaques and tangles in the symptoms of Alzheimer's disease is also unknown. At the same time, however, various components of the cholinergic transmitter system may be partly related to plaque formation, and the cerebral cholinergic system has been linked with many behavioral patterns (such as sleep and arousal) that are frequently disturbed in Alzheimer's disease. Professor Tomlinson goes on to assert that there is no certain relationship between tangle formation, on the one hand, and either neuron loss or dendritic abnormalities demonstrated in normal aging and demented subjects, on the other. Thus, he concludes, continued investigation into the roles of plaques and tangles remains a major challenge in research into dementia and aging.

A second major purpose of these editorials is to question the validity of interpretations that have come to be fashionable. James Shields, for example, questions whether childhood differences found between groups judged to be at high and low risk for schizophrenia are actually related to greater risk of schizophrenia or, rather, "to the quality or lack of family life which is hard to match experimentally" (p. 60). Dr. Shields goes on to suggest that many of the experimental variables thought to indicate increased risk for schizophrenia, such as disordered attention, may be nonspecific for schizophrenia—hence, the need for follow-up studies to better establish the predictive validity of such experimental variables.

In general, readers will find that the contributions to this volume are tersely written and extensively referenced. Indeed, given the constraints of space inherent in a commissioned editorial, some of the reviews will be considered elliptical. Another difficulty inherent in an undertaking like this relates to the rapidity of progress in different fields of psychiatric research; thus, many of the contributions in this volume, which are already 8 to 12 years old, might be viewed as outdated or, at the least, of limited value to clinicians wanting to update their stores of current information and of equally limited value to investigators seeking to formulate state-of-the-art, sharply focused research questions. Another aspect of this volume limited my enthusiasm for it: whether intended or not, in its emphasis on setting forth the boundaries of our ignorance, progress in psychiatric research is given short shrift. Readers may come away feeling that psychiatry is a rather more dismal science than it actually is or than other parts of medicine are. To the extent that the book creates such an impression, it does a disservice to the enterprise it seeks to advance. In essence, this volume conveys little of the excitement and progress of contemporary psychiatric research.

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Review of General Psychiatry, *edited by Howard H. Goldman, M.D., M.P.H., Ph.D. Los Altos, Calif., Lange Medical Publications, 1984, 676 pp., $24.00 (paper).*

> Critics in neuroscience characterize psychiatry as brainless; critics within psychological medicine fear that psychiatry will become mindless. Students everywhere are concerned that the curriculum not be witless. Our aim is to present psychiatry with the proper mix of brain, mind, and wit. (Preface)

Like good therapists in the initial psychiatric interview, the many authors included in this book establish an alliance of

sorts with the reader, a "pedagogic alliance" that allays anxieties, overcomes resistances, and fosters motivation to further explore the material. As the above excerpt portends, this *Review* has sacrificed neither content nor style for the sake of the other and succeeds admirably as a straightforward, highly informative, and lively text. It is a well-executed and balanced work that constitutes a step forward in psychiatric medical education.

The book consists of 60 chapters by individual authors, most of whom are from the faculty of the University of California, San Francisco, School of Medicine. Despite the hazards of multiple authorship, the style and level of complexity are almost uniform, and redundancy is minimal. The first 16 chapters deal with theoretical and conceptual issues, the basic sciences of psychiatry and human behavior, and introductory developmental theory. The following seven chapters describe the psychiatric assessment, including techniques of psychiatric interviewing, the mental status examination, psychological testing, and how to write a comprehensive case formulation. These chapters are nicely integrated by means of an in-depth case history that unfolds across several chapters. A most welcome innovation is an entire chapter devoted to the physical examination and laboratory investigation, a recognition that these medical procedures are essential elements of the complete psychiatric assessment.

The next 18 chapters present the mental disorders, following the general format of *DSM-III*. Noteworthy is the chapter on personality disorders, which presents each of these disorders not only as it manifests itself in psychiatric practice but also as it may appear to the internist dealing with a medical inpatient. This chapter is one of the means by which this book succeeds in bridging specialized psychiatric knowledge with meaningful and commonly encountered issues in general medicine.

The final 19 chapters concentrate on treatment modalities, including a chapter on psychotherapy with chronically medically ill patients. The chapters on psychopharmacology deal with basic pharmacology in addition to the usual and customary charts of dose ranges, equipotency, and side effects of the psychotropics and will therefore be useful as reviews for more advanced readers. There are also overviews of special topics and settings such as forensic psychiatry, psychiatric emergencies, and consultation-liaison psychiatry.

Compared with other texts used by medical students, including those on which I cut my teeth, I found the *Review* to be better organized and better written. It is neither discursive and impressionistic like *The Harvard Guide to Modern Psychiatry* (1) nor so somber as *Modern Clinical Psychiatry* (2). Medical students will find this book useful during their basic science training in human behavior as well as during their clinical rotations. Psychiatric residents will want to acquire this work as a review and reference text. And the chapters on personality disorders in the medical setting and psychosomatic medicine ensure that the *Review* will respectably represent our discipline to our nonpsychiatric colleagues as a field with specialized knowledge of its own, yet closely integrated with the understanding and treatment of medically ill patients. A caveat to those interested in acquiring this book, however, is that a second edition is planned for publication this year. Potential buyers may therefore wish to postpone their purchase.

Textbooks, as a rule, do not break new ground in theory or research and are therefore often expected to be dull and pedantic. Although *Review of General Psychiatry* is no hotbed of clinical controversies, no glitzy starlet, it is a solid, steadfast workhorse girded for the long haul. I hope its crimson cover becomes a familiar occupant of overstuffed book bags of medical students throughout the land.

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A Method of Psychiatry, 2nd ed., *edited by Stanley E. Greben, M.D., Vivian M. Rakoff, M.B., B.S., and George Vioneskos, M.D. Philadelphia, Lea & Febiger, 1985, 447 pp., $29.75.*

This is the second edition of a textbook of psychiatry intended primarily for medical students and written by the faculty of the Department of Psychiatry of the University of Toronto. The "method" suggested by its title is "a broadly-based eclecticism which uses the contributions of many different points of view in the field of psychiatry" (p. v). Indeed, the book does strive for comprehensiveness and is meant to be useful in the preclinical years and during the psychiatry clerkship. It comprises 41 chapters divided into six major sections: Life Stages and Illness, Psychobiology and Medicine, Psychiatric Illness (presented in a *DSM-III* format), The Patient and the Physician, Treatment and Management, and Special Problems.

There is actually very little to fault in this textbook. The chapters are fast moving, well written, and fairly current and complete (notable exceptions are the very incomplete coverage of panic disorder and the failure to mention family treatments for schizophrenia). The editors have generally, but not always, succeeded in eliminating redundancy. The problems with the book are the usual ones for this format—the presentations vary in quality and most are kept at quite a superficial level, even for a medical student audience. My only disappointment with the book was occasioned by its failure to deliver on its promise of providing a "method of psychiatry." It is certainly no more methodical, integrative, systematic, or pluralistic than other available textbooks. This is a book that students and teachers will find useful but not enthralling.

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Letters to the Editor

Convulsions in Patients Abruptly Withdrawn From Clonazepam While Receiving Neuroleptic Medication

SIR: The use of clonazepam, a potent benzodiazepine and γ-aminobutyric acid (GABA) agonist, in the treatment of psychiatric patients has been increasing. Clonazepam is known as an anticonvulsant; its use in mania (1) and other psychiatric disorders has only recently been explored. Because it is often used in combination with neuroleptics, its withdrawal effects can be serious. We report three cases in point.

Ms. A, a 31-year-old hypomanic woman, was hospitalized and began to receive clonazepam, 6–10 mg/day, and carbamazepine, 400–600 mg/day. Eight weeks later, she began receiving trimipramine, 150–200 mg/day, while the clonazepam was decreased to 4 mg/day over several days and then discontinued. Five days after the clonazepam was discontinued, she received chlorpromazine, 200 mg, for agitation. The following day she developed a grand mal seizure, which was confirmed by an EEG. She had no history of seizures. One-year follow-up showed no further seizures despite later resumption of neuroleptic treatment.

Ms. B, a 48-year-old woman with a history of psychotic depression, alcoholism, and seizures, was admitted to the hospital in an acute psychotic state. For 3 weeks she received clonazepam, 2 mg p.r.n.; she then received 8 mg/day for 4 days, after which the clonazepam was discontinued and chlorpromazine, 400–600 mg/day, was resumed. Three days later, because of her acute psychotic agitation, which was not responsive to chlorpromazine, she was started on haloperidol, 10 mg every hour, with three consecutive doses until 1:00 p.m. Shortly thereafter she developed a generalized motor seizure that lasted 2 minutes, followed by postictal confusion. She responded to pain and had hypertonia and hyperreflexia in the limbs, associated with extensor plantar responses. An EEG showed nonspecific slow waves in the left temporal area. She was treated with an anticonvulsant and stabilized. Probably the synergetic effect of two neuroleptics in the absence of clonazepam precipitated the epileptic seizure.

Mr. C, a 25-year-old man, was hospitalized for an acute psychotic state and aggression. Because of his poor response to neuroleptics, megadoses of diazepam (520 mg/day) were tried, but without success; these were gradually discontinued and he began taking clonazepam, 8 mg/day, with fluphenazine HCl. This regimen continued for about a month and was then discontinued. Mr. C was started on thioproperazine, 15 mg/day, but he became more violent and required 300 mg of chlorpromazine 3 days later. The following morning he developed a generalized seizure and was given diazepam, 20 mg/day, with no neuroleptics. A week later the thioproperazine was resumed, and Mr. C recovered without any further seizures.

Clonazepam has an eliminating half-life of 20–40 hours; it suppresses paroxysmal EEG activities (2), while neuroleptics lower the seizure threshold. Although seizure due to clonazepam withdrawal is known to occur in epileptic patients (2), we could find no specific reference on the subject with respect to a psychiatric population. The anticonvulsive properties of clonazepam probably protect neuroleptic-treated patients against seizure. Hence, when clonazepam is given in combination with neuroleptics or antidepressants, its abrupt withdrawal removes this protection and exposes susceptible patients to convulsions. Marks (3) wrote that neuroleptic-benzodiazepine combination treatment carries such a risk. We propose gradual and cautious discontinuation of clonazepam, particularly in patients with histories of seizure, alcoholism, and organic brain syndromes. Special attention is required when clonazepam withdrawal is considered after combination treatment with neuroleptics or tricyclic antidepressants.

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Phencyclidine and "Crack"-Precipitated Panic Disorder

SIR: We read with considerable interest the report by Thomas A. Aronson, M.D., and Thomas J. Craig, M.D., M.P.H., on cocaine precipitation of panic disorder (1). Recently we treated two patients whose panic attacks were precipitated by the use of recreational drugs. In one patient, the panic attacks were precipitated by the use of cocaine in the form of "crack," in much the same manner as they were in the patients described by Drs. Aronson and Craig; in the second patient, the panic attacks started after the use of intranasal phencyclidine (PCP). We briefly report the case of PCP-induced panic disorder and discuss its impact on our understanding of panic disorder.

Mr. A, a 31-year-old white male, presented with a 4-year history of panic disorder. He could trace the onset of his panic attacks to a 2-month period when he had been snorting PCP daily. Before this time his use had been restricted to once or twice weekly. He had been using PCP for 3 years at that time and preferred it to cocaine because of its varied effects and more reasonable price. During this period of heavy use, he had experienced an attack of chest pain, palpitations, shortness of breath, and diaphoresis.

He had had a fear of imminent death and, in fact, had feared that he was having a heart attack. Over the next several weeks, each time he snorted PCP he would experience a similar episode of extreme panic. He eventually stopped taking PCP, but the panic attacks persisted and gradually increased in frequency to their present state of three per week. He denied the use of other drugs or alcohol but admitted becoming intolerant to caffeine over the past 4 years. Avoidance of shopping malls and crowded stores subsequently developed. Mr. A denied a past psychiatric or medical history and had no family history of psychiatric illness. He was treated with desipramine, 150 mg/day, and the panic attacks subsided, as well as some of the faint cravings he had for PCP.

As Drs. Aronson and Craig pointed out, chronic cocaine use can lead to a variety of neurochemical changes that may be responsible for the development of panic attacks. Increased β-adrenergic, α-adrenergic, and dopaminergic receptor binding all occur with chronic cocaine use. The neurochemical changes attributable to chronic PCP use are less well defined, although PCP has been shown to possess physiological and physical properties similar to those of cocaine (2). It has been demonstrated that PCP releases dopamine and norepinephrine presynaptically (3) and that it is as potent as amphetamine in blocking catecholamine reuptake (4). Certainly PCP and cocaine in the form of "crack" need to be added to the growing list of substances capable of producing autonomous panic disorder, and the research that Drs. Aronson and Craig suggested should be broadened to include these drugs. Our case and the three presented by Drs. Aronson and Craig raise some important questions regarding our understanding of the development of panic disorder and reaffirm our belief that recreational drugs carry a price that goes far beyond the cost of the drugs themselves.

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Imipramine Treatment of Agoraphobia

SIR: In the article "Two-Year Follow-Up of Exposure and Imipramine Treatment of Agoraphobia" (1), the authors described the drug conditions as double-blind. This merely represents their statement of intent, because no data are presented to show that the study was double-blind in fact, as distinct from in conception. Thus, neither the researchers nor the patients were asked to guess the drug status of the patients during the study, even though in an earlier report (2) the imipramine group had been found to experience significantly more side effects than the placebo group after 1 and 3 months of treatment. Such a difference may have vitiated the notion of a double-blind design, allowing the expectations and wishes of the participants to prevail.

It may not be irrelevant that the beneficial effects of imipramine and of imipramine and flooding were present at the 1-month review, that is, some 14 days after the drugs had been tapered and discontinued, but were not present at the 6-, 12-, and 24-month reviews.

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Thiamine Deficiency and Psychosis

SIR: We would like to report on a patient with psychosis related to thiamine deficiency; she responded to intramuscular administration of thiamine, with complete resolution of symptoms in 48 hours. Thiamine deficiency is known to cause Wernicke-Korsakoff syndrome; however, complete recovery in 48 hours is exceptional (1).

Ms. A, a 36-year-old housewife, was brought by police to the psychiatric emergency room because she had stabbed herself in the chest. On mental status examination, she was extremely agitated and appeared to be responding to hallucinations. She called herself "Satan" and wanted to hurt herself. According to her family, this behavior had started 2 days earlier and had been steadily getting worse. She was admitted to the medical psychiatric unit with a diagnosis of atypical psychosis and was initially treated with 15 mg/day of haloperidol and 4 mg/day of trihexyphenidyl HCl in divided doses. Her mental status and behavior continued to deteriorate, requiring use of parenteral haloperidol, seclusion, and restraints. Three days after admission, Ms. A experienced a grand mal seizure. At this time the haloperidol and trihexyphenidyl HCl were discontinued and a neurology consultation was ordered.

Results of a physical examination, including a detailed neurological examination, were essentially normal except for nystagmus. The laboratory examination revealed a WBC of 12,000/mm^3 with normal differential count, normal levels of vitamin B_{12} and folic acid, an SGOT of 73 U (normal range=5–42), normal calcium and magnesium levels, and normal levels of electrolytes and glucose. Results of a subsequent CAT scan and EEG were also normal.

At this time, the family gave some history of alcohol abuse by Ms. A; thus, the possibility of alcohol withdrawal seizure was discussed. She was started on diazepam, 20 mg/day, and remained stable for the next 2 days, with no real improvement in her mental status. On the 3rd day after the seizure, thioridazine, 200 mg/day, was added, and the diazepam was gradually withdrawn. She remained

delusional and confused and continued to experience hallucinations. At this time an alternative etiology of psychosis was discussed.

On the 8th day after admission, thiamine, 100 mg/day i.m., was added to the regimen. Ms. A responded to the thiamine in 24 hours, with partial clearance of her psychosis. At the end of 48 hours, she had no evidence of psychosis. She acknowledged her drinking problem in subsequent interviews. She was discharged on maintenance doses of thiamine, 100 mg/day p.o., and thioridazine, 200 mg/day.

Confusion, altered consciousness, nystagmus, and ophthalmoplegia constitute the picture of Wernicke's encephalopathy, while memory disturbances and confabulation are the hallmark of Korsakoff's psychosis. Korsakoff himself appreciated that the mental symptoms could occur without classical Wernicke's features, and, similarly, memory problems in Korsakoff's psychosis can present in a number of attenuated forms. This syndrome can occur in chronic alcoholics and has also been described in severe diseases of the gastrointestinal tract such as carcinoma and regional enteritis. Parenteral administration of thiamine prevents the development of Korsakoff's psychosis and helps resolve the symptoms of Wernicke's encephalopathy. This case report should remind psychiatrists of the variety of possible etiologies of psychotic behavior; thiamine deficiency is one of them.

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Treatment of Agitated Depression With Alprazolam

SIR: Regarding the recent paper by Jeffrey P. Kahn, M.D., and associates (1), we wish to report a similar rapid response to alprazolam in a patient with marked agitation and severe depression.

Ms. A, a 45-year-old woman, had a 6-month history of moderate depression with symptoms of depressed mood, anhedonia, anergia, and difficulty concentrating. She had had no previous psychiatric difficulties, although her father had bipolar illness. Two weeks before her first hospitalization, she became considerably worse, with psychomotor agitation intermixed with retardation. She was treated as an outpatient, but trials of amitriptyline and maprotiline had to be discontinued before effective doses could be reached, because of anticholinergic and allergic side effects, respectively. Upon hospitalization Ms. A was started on phenelzine, with eventual additions of liothyronine and lithium. Seven days after initiation of the phenelzine, she was transferred to a different hospital. On admission to that hospital she was severely depressed, with prominent psychomotor symptoms. She had difficulty talking and spent most of her time either in bed in the fetal position or pacing.

She was evaluated for ECT, and the phenelzine was discontinued. She received thioridazine, up to 150 mg/day, for relief of agitation for 3 days with no benefit. The thioridazine was then discontinued, and alprazolam, 1 mg b.i.d. orally, was started. She improved rapidly over the next 4 days. She dressed herself without assistance and spontaneously smiled and socialized with ward staff and patients. Upon discharge she had a complete remission of psychomotor symptoms, although she remained mildly depressed. She was discharged on a regimen of alprazolam, 1 mg t.i.d. orally, and her depressed mood improved further over the next month. She continued to take alprazolam for 6 months, and then it was discontinued. She has remained well in the 2 years since then.

Similarities in the presentation of this patient to those described in the report by Dr. Kahn and associates include the marked agitated component of the depressive disorder and the rapid response to alprazolam. The rapidity of response was so dramatic that we considered the possibility that it was a placebo response, although Ms. A had been severely depressed upon admission and had failed to respond to other antidepressants and neuroleptics, albeit in less than adequate trials. Separation issues were also involved in this case. Our patient had initiated a marital separation upon hospitalization and eventually went on to divorce her husband after recovering from the depression. Unlike two of the patients in the report by Dr. Kahn et al., however, there was no previous history that suggested panic disorder, and the onset of the depression was characteristically slow and progressive. The family history of bipolar illness and the patient's persistently high energy level after the disappearance of her depressive illness raised the possibility of bipolar illness. However, Ms. A at no time had a sufficient number of symptoms for the diagnosis of mania or even hypomania. The response of this patient and the report of Dr. Kahn and associates suggest that alprazolam may be worth considering as a treatment for patients who have agitated depression with or without a history of panic disorder.

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More on Psychiatrist-Patient Sexual Contact

SIR: We read with great interest the report by Nanette Gartrell, M.D., and associates (1) on psychiatrist-patient sexual contact. Despite the limited return rate (26%) of their questionnaire, the authors discussed several factors that supported the validity of their findings, including results of similar surveys of other professional groups.

In further support of the validity of their results, we report findings from a survey on psychiatrist-patient sexual contact that benefited from a much higher return rate (58.6%). In 1980–1981, the Washington Psychiatric Society (WPS), a district branch of the American Psychiatric Association, surveyed the entire WPS membership (N=1,060) on this topic. The WPS survey's return rate—which is considered very high for studies of this kind—probably resulted in large part from the institutional, as opposed to private, sponsorship of the survey.

As in the study by Dr. Gartrell and associates, we found in the WPS study that the sex and age distribution of the respondents closely paralleled those of the entire population sampled, which enhances the validity of our results. In the WPS study, 7.9% of the male, 2.2% of the female, and 6.6% of all the respondents acknowledged sexual contact with their ongoing or former patients. (If posttermination cases are excluded, the overall rate drops to 6.1%.) The WPS findings correspond closely to those for the nationwide study by Dr. Gartrell and her colleagues, who reported 7.1%, 3.1%, and 6.4%, respectively. More than 90% of the self-acknowledged offenders in both studies were male, and the patients were predominantly female.

In addition, we explored attitudes of offenders and nonoffenders toward sexual contact with patients. Of the self-reported nonoffenders, 79% of the men and 97% of the women stated that psychiatrist-patient sexual contact is "always harmful." In contrast, only 60% of the offenders believed that such contact is always harmful; among the 40% of the offenders who were unclear about the negative consequences of their behavior, there were rationales that sexual contact "can be used, if explored," that it is "beneficial, to work through exhibitionistic defenses," and that such contact is not really sexual but is "loving."

By better understanding the patterning of attitudes and common sources of confusion—and perhaps, by examining offenders' rationales—we can begin to design more effective programs aimed at intervention. The urgent need for this type of work is demonstrated by the fact that nearly two-thirds of the WPS survey respondents requested more detailed and specific recommendations about psychiatrist-patient sexual contact. Among the five common areas of confusion that we identified in the WPS survey, the greatest questioning and desire for clarification centered on 1) issues about sexual contact with former patients and 2) concerns about the adequacy of current mechanisms for reporting suspected offenders.

By gathering reliable data in a nationwide survey, Dr. Gartrell and her associates have taken a critical step toward both defining and addressing the problem of psychiatrist-patient sexual contact. We look forward to their discussions of posttermination sexual contact and other issues. Perhaps the greatest clarity and change, however, will come not just from elaborating more detailed rules but from better educating psychiatrists about the harmful sequelae of all forms of sexual abuse, including the damage that comes from the therapist's sex-related betrayal of trust, which impairs the patient's ability to seek or to form future therapeutic relationships.

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SIR: In an earlier age, to say that sexual contact between a psychiatrist and a patient was sinful would have sufficed as an explanation of what is wrong with this behavior. To Aquinas, sin suggested particular, and particularly appalling, acts of pride, covetousness, lust, gluttony, envy, anger, and sloth. These are the seven mortal sins—those deadly to spiritual well-being, damaging to the soul, or, as we now say more timidly and less robustly, damaging to persons. Sin is not merely an endearing character weakness but a violation that victimizes someone else while implicating and impugning the sinner as well.

If one is constrained to choose from among the deadly sins the one that is most likely to illuminate the practice of psychiatrist-patient sexual contact, "lust" recommends itself immediately. According to the study by Dr. Gartrell and her associates, what is wrong in the sexual encounter governed by lust is that the patient is used by the therapist for his own pleasure. (I use the masculine pronoun advisedly, because the study found that 88% of reported sexual contacts occurred between male psychiatrists and female patients.) But what are we to make of the minority of therapists who claim that it is not their own pleasure but the patient's benefit that they seek? Taking these psychiatrists at their word, lust is disqualified. However, covetousness may apply. Covetousness, too, has to do with inordinate desire, the end in view being not pleasure but acquisition. One wishes to own, to *have*, the patient's betterment. It was just such possessiveness that Freud warned against when he consistently and emphatically rejected "the view that we should convert into our own property the patient who puts himself into our hands in search of help. . . . This is only tyranny, even though disguised by the most honourable motives" (1).

How, then, is the therapist to behave? Freud's views on transference are instructive. The transference is a vehicle for the transformation of the passions (in Freud's view, chiefly the passion of dependence). It "forms a kind of intermediary realm between illness and real life, through which the journey from the one to the other must be made" (2) This being so, for the therapist to step out of the temporary and artificially constructed fire-free zone that is the therapeutic encounter into the real and troubled world of the patient for any reason whatever is an overreaching of legitimate authority and is countertherapeutic to boot.

As a breach of the psychiatrist's professed intentions in the therapeutic encounter, psychiatrist-patient sexual contact is unethical because it undermines the trust that drives the therapy. (In Gartrell and associates' survey, the majority of the psychiatrists who had been sexually involved with their own therapists said they had felt exploited and harmed.) It is countertherapeutic because it is likely to exacerbate or at least prolong the patient's distress by transferring his or her dependence from one artifact of neurotic attachment (the one at the source of the illness) to another (the therapist's person rather than his or her role). Do we need the language of sin to say these things? Probably not. That language does not resonate as richly as it once did. But for the patient's sake, we do need to be able to articulate as clearly as Aquinas why covetousness in all its forms is unethical and as clearly as Freud how the transference, when corrupted by covetousness, is also countertherapeutic.

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Reporting the Proportions of Variance Explained (PVE)

SIR: Much of the impressive progress in psychiatric research during the past two decades has been due to the profession's adoption of increasingly more rigorous experimental methodologies and sophisticated approaches to statistical analysis. With regard to describing statistical procedures, the *Journal* currently requires authors to report the names of the tests used with each set of data, whether the test was one-tailed or two-tailed, standard deviations along with means, actual test values (t or F), degrees of freedom, and appropriate alpha levels. Such information is necessary for the reader to assess the appropriateness of the statistical analysis and usually provides adequate information for judging whether chance or random variation may be excluded in accounting for any observed effects.

A problem arises when "statistical significance" is reported, because the reader has no grounds for evaluating the substantive importance of an outcome. Any trivial difference or correlation may, if the degrees of freedom are high enough, achieve statistical significance. We suggest that this journal and other psychiatric research journals adopt a further convention in statistical reporting: the proportion of variance explained (PVE) by a statistically significant result. Reporting the PVE aids in placing statistical significance in proper perspective and helps the reader to avoid confusing statistical significance with meaningful effects. For example, if an author reports the results of an overall analysis of variance as $F=14.8$, $df=3, 984$, $p<.0001$, the reader may conclude that important differences were detected. Yet the PVE in this example is only 4.32%! Since more than 95% of the variance in the dependent variable is not accounted for by this statistically significant result, it may be difficult to ascribe any substantive importance to the effects. Instructions for calculating the PVE for common parametric and nonparametric tests are readily available (1–3). Until journal editors require reports of PVE, readers may perform such calculations for themselves, providing an article includes t, F, or chi-square values and degrees of freedom. We have described elsewhere (4) the simple calculations that are involved.

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Growth Hormone Response to Clonidine in Depression

SIR: There are some methodological issues worthy of comment in the study on the human growth hormone (GH) response to clonidine by Raymond J. Dolan, M.B., M.R.C.Psych., and Stephen P. Calloway, M.R.C.P., M.R.C.Psych. (1). These are related to the central aim of the study, which was to test Matussek's demonstration in 1980 of an impaired GH response in patients with endogenous depression; this finding was replicated and a report was published by Checkley et al. in 1984 (2), but it was not referred to in the article by Drs. Dolan and Calloway. The finding is important to verify, because preliminary evidence from recovered, unmedicated, endogenously depressed patients suggests that the abnormality persists and may represent a trait marker for this disorder (unpublished data of P.B. Mitchell, J.A. Bearn, T.H. Corn, et al.).

The use of the thyrotropin-releasing hormone (TRH) challenge 2–3 hours before the clonidine challenge is of concern. Although the authors did not note any GH response to the TRH, there is some evidence (e.g., 3) suggesting that TRH affects central noradrenergic activity. This is particularly pertinent to the GH response to clonidine, which appears to be mediated by α_2-adrenoceptors. Another factor possibly affecting α_2-adrenoceptor function in this particular study was the use of a drug-free washout period of only 2 weeks. Previous studies of the GH response to clonidine have used a minimum drug-free interval of 3 weeks, since the desensitization of α_2-adrenoceptors by tricyclic antidepressants persists after drug withdrawal for at least this long and perhaps for even 6 weeks (4).

The other major methodological problem was the failure to match the endogenous and nonendogenous groups for age and sex, as these are important factors in GH secretion (2). Without matching, it is not surprising that the study of a total sample of only 14 subjects was unable to demonstrate a significant difference between the two subtypes of depression.

The finding of a significant negative relationship between predexamethasone urinary free cortisol levels and GH levels is of interest with respect to the putative abnormal physiological mechanisms occurring in depressive illness. The hypothesis that subsensitive α_2-adrenoceptors account for the blunted GH response to clonidine suggests either a primary abnormality or a downregulation secondary to increased synaptic noradrenergic activity. With regard to increased hypothalamic-pituitary-adrenal axis activity, one of us (G.A.S.) has found in rodents that 1) stress-induced ACTH and cortisol production are closely associated with increased noradrenergic activity in the medial basal hypothalamus (5) and 2) increased hypothalamic noradrenergic neuronal activity is also associated with GH inhibition (6). This suggests that an increase in hypothalamic noradrenergic activity may account for the association of these abnormal findings in depressed subjects.

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More on the Empiricist and His New Clothes

SIR: The criticism of *DSM-III* by David Faust, Ph.D., and Richard A. Miner, M.D., in "The Empiricist and His New Clothes: *DSM-III* in Perspective" (1) was misdirected. Agreeing that it is "difficult to classify" the precise methodological approach or underpinnings of *DSM-III,* they criticized its empirical bias, arguing that "emphasis on description is a throwback to Baconian science" and that the goals of reduction of inference and theory and the emphasis on description "should not be pursued."

They have attacked *DSM-III,* when their real target is empiricism in psychiatric practice and thinking today. Inference is used at every turn in the clinical psychiatric evaluation as well as in the development of understanding based on psychiatric research. Our antidepressants, for example, are not illusory, nor is our understanding of mood disorders atheoretical. The use of a theoretical framework in *DSM-III* is very clear in the case of the organic mental disorders; e.g., the neuropathological basis for the dementias is not a product of a purely descriptive approach. One of the examples chosen by Drs. Faust and Miner to point up the "illusory" aspect of objectivity was the use of an IQ of 70 as a rigid cutoff point for mental retardation. They clearly ignored the intent of *DSM-III,* as stated in the manual, which is that "an IQ of 70 is considered to represent a band or zone of 65 to 75" and that the number is to be put aside in the face of judgmental considerations. There is a need to communicate an observation about a patient's level of intellectual functioning without having to cite or review the "hundreds of articles" that are known to exist on IQ measurement and its uncertainties.

Drs. Faust and Miner are concerned that an empiricist approach in *DSM-III* will prematurely exclude further scientific development. *DSM-III,* however, is not a total statement of the field and philosophy of psychiatry, nor does it prevent psychiatrists from considering other diagnostic categories. I would suggest that *DSM-III* is not an empiricist philosophy of psychiatry but is, rather, a tool for the communication of information and the facilitation of a shared frame of reference among diagnosticians. Empiricism, which the authors attacked, is not a label that can be applied wholesale to *DSM-III.* I suggest another underlying orientation for *DSM-III* and perhaps even *DSM-IV,* namely, common sense. A classification of disorders in psychiatry must inevitably bring together categories that are well understood etiologically and entities that are more poorly defined. Furthermore, as in the case of substance use and abuse, changing fashions and effects of exogenous factors will produce new entities and descriptions.

Drs. Faust and Miner have pitted the need for creative thinking in psychiatric research against the need for definitions in communicating the findings (illusory or otherwise) of everyday psychiatric practice. It is not a question of either/or but rather of the judicious use of intellectual tools for appropriate tasks. Our field needs to progress by means of wide-ranging research and untethered pursuit of new ideas, while the everyday practice of humane patient care requires precise tools of communication.

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SIR: The first sentence in the article by Drs. Faust and Miner reads, "There are many positive features of *DSM-III* that one can address, but the purpose of this article is not to do so." Had they stopped here, their purpose admirably accomplished, there would have been no need to write this letter. But, alas, they chose to go on, and in a pastiche of paralogical ideas they tried to make their case.

There is, for one example, no logic in the implication that *DSM-III* is against the development of creative theory or thinking because its nosology was based on an atheoretical foundation. One need only examine this and other psychiatric journals to see that research, new ideas, and theories have in no way waned since the acceptance of *DSM-III.* Witness, for instance, the plethora of articles on borderline personality disorder in recent years. Nowhere in *DSM-III* is it implied or suggested that creative thinkers should desist for lack of specific instrumentation. The future Einsteins and Galileos of our field are not in a *DSM-III* straitjacket, nor do the founders of *DSM-III* claim anywhere that facts are theory neutral. Drs. Faust and Miner, in their eagerness (however Procrustean) to connect Sir Francis Bacon with *DSM-III,* force unfounded philosophical errors on these founders that are simply unwarranted.

Further, it is not logical to hint that reliability—given a high priority in *DSM-III*—impedes the flow of progress in our field. I agree with the authors that unreliable observations should be given their just due. Again, one need only read the literature and listen to the rhetoric to see that speculation and theorizing are as healthy as ever.

My point, then, is that the authors lost perspective in their article. They have a valid philosophical view of science, but it has very little to do with *DSM-III.* My bet is that the developers of *DSM-III* had not read Francis Bacon at all, because, if they had, they would have discovered that he opposed theory not one whit.

My prejudices are these: *DSM-III* is not perfect, but it represents real progress in a nosology that will enable us to talk in a common language, and although I cannot prove it, no good theory was ever developed that was not in some way based on prior observation, however remote from the final theory.

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SIR: Drs. Faust and Miner inveigh against the empiricism and descriptive nature of *DSM-III* by emphasizing that all empiricism is based on some theory. This is true, but they focus on a peripheral point and miss the main one. The assumption underlying *DSM-III* is that the diagnosis of a mental disorder should be empirically useful to the clinician, whether the basis for usefulness is known or not. If I diagnose this or that disorder in a patient, will I be better able to predict prognosis, response to treatment, or some

such important fact? To say that all facts depend on some theory is, in this context, not very important. Most of the major diagnoses of *DSM-III* have been used successfully to predict some important fact. The response of patients to imipramine will differ according to whether the diagnosis is major depression or schizophrenia. If there is a different categorization that can improve our predictions, it should be proven.

My complaint about *DSM-III* would be the opposite: it isn't empirical enough. Many categorizations do not have empirical support. For example, why is it important to distinguish nonsocialized from socialized aggression in conduct disorders? It seems sensible to think that such patients might be different, but do we know?

I offer a challenge to Drs. Faust and Miner. Taking all their theoretical concerns into account, can they provide a more useful schema? Their statement that multidimensional ratings are as good as typological categories is just not so. For example, drug-placebo differences have been widely shown when typological diagnoses are used. Where are the comparable data for multidimensional categorizations?

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Dr. Faust Replies

SIR: Space limitations permit only selective comments on the complicated and interesting points raised by Drs. Hankoff and Spital. These obviously thoughtful and scholarly individuals were, of course, equally handicapped by these limitations.

Their comments notwithstanding, I remain comfortable in characterizing the aims, or underlying prescriptive framework, of *DSM-III* as most closely matching classical empiricism. I would once again note, for example, the *intention* to minimize inference and emphasize description, to use operational definitions, and to create a common base of diagnostic categories that will serve as the "observation language" for the accumulation of knowledge. I do not say the match is perfect, but in contrast to *DSM-II,* the move is obviously in this direction.

Both writers argue that Dr. Miner and I have misconstrued *DSM-III;* i.e., the document is not "empiricist," or its intention is a focused one, namely, to offer a means for communication among diagnosticians. I certainly agree that empiricist aims were not accomplished. Our point was that these aims were prescriptive, or viewed as "oughts" or goals. They were not accomplished because they cannot be accomplished. I would also ask Dr. Hankoff whether his separation between a method of communication and a means or method for broader purposes is either as obvious or as conceptually or practically simple as he seemingly implies. I know from personal conversation that at least some *DSM-III* task force members viewed classical empiricism as the superior approach to science in general. In addition, is it really correct to think that the observation language for diagnostic classification which *DSM-III* outlines is merely a tool for communication and exists independently of other practices, thoughts, or constructs? Many journals are likely to prefer manuscripts that use *DSM-III* diagnostic criteria, and these classifications will often determine how subjects are grouped in studies and thus affect the results obtained. Also, as scholars such as Bunge (1) have cogently argued, the object language is never independent of other components of scientific thought or theories, and the tools of "communication," whatever they may be, are packed with assumptions about how the world is to be studied or viewed. *DSM-III* does not use such phrases as "a schizophrenic," but rather, "a person with schizophrenia." This is almost surely a plus, but the point is that the tools of communication, or the language that is used, inevitably reflect conceptualization.

Dr. Hankoff also argues that the underlying orientation is not empiricist but "common sense." If this is a more apt characterization than empiricism, it should hardly make us breathe easier. It might be tempting to contrast common sense with nonsense, but the relevant comparison is between common sense and science. The whole point of the scientific enterprise is to go beyond and to correct common sense, as required. If our science cannot do this, it has done nothing to justify its label.

Both commentators seemed to miss a major point that we emphasized repeatedly in our article. We were particularly concerned with potential consequences should *DSM-III*'s methodological trends be taken to an extreme. *DSM-III* certainly could represent a march in this direction, one that easily could go too far. Is this concern legitimate? This was the destructive trap into which mainstream psychology fell at an earlier time and from which it has not yet completely emerged. In reaction to the "loose" science that seemed rampant, psychologists tried to attain instant scientific credibility by wholeheartedly adopting the philosophy of classical empiricism or positivism. Ironically, although psychologists thought they were modeling hard science and that the yield would be substantial, what they actually adopted was a philosophical caricature of science that, even at that time, was rapidly diminishing in status. Psychologists failed to realize that rigor and precision could not be bought so cheaply and that it was not method per se but almost 300 years of struggle—and perhaps a subject matter much more tolerant of simplification—that led physicists to achieve greater exactness and predictive power.

A very positive feature of *DSM-III* is the attempt to be explicit and to create diagnostic entities that are more amenable to scientific testing and disproof. A characteristic of more mature science, although by no means the only one, is the decreased time span for rendering prior knowledge obsolete. That a draft of *DSM-III-R* has been devised is testimony to progress in this regard.

These statements may seem to conflict with certain implications that could, but should not, be drawn from our original article. There is nothing inconsistent in arguing against classical empiricism or premature rigor and arguing for the "testability" of scientific propositions and other forms of "quality control." An argument against classical empiricism is not an argument for anything that contrasts with it, especially certain habits that have been a bane to progress, e.g., sloppy thinking, feeble inferences, theories that can be supported no matter how the data turn out, and outright rejection of research findings. We would be alarmed if our article were used to justify such habits or a retreat to commitment in which one claims exemption from the effects of counterevidence. Innovation is rare and precious, but theoretical proposals demand careful scrutiny and both empirical checks (i.e., data) and nonempirical checks (e.g., analysis of logical adequacy, promise for generating fruitful research). In other writings (2–4) I have emphasized the prevalence and risks of problematic thinking habits in research and clinical practice and have offered corrective suggestions.

Aristotle wisely stated that it is the mark of the educated

person to adjust the precision of measurement or method to that which the subject matter permits. My major concern involves the possible endpoint in the ongoing transformation of the scientific authority structure in psychiatry. The shift is toward greater emphasis on rigor, and this can be beneficial if not taken too far. What is too far? Classical empiricism certainly is too far, especially if those who do not embrace it are expected to conform nonetheless. Our primary intent, as stated in the original article, was to promote a broad and balanced perspective. Diversity and open exchange among those with competing views and approaches are essential to scientific development. A too narrow authority structure that prohibits too much, as would occur through extension of classical empiricism and as did occur in psychology, could be very destructive. To promote progress we must protect contexts that allow for open exchange (5). Encouraging or supporting diversity, which is not to be confused in any way with encouraging retreat from scientific accountability, is one way to provide this needed protection.

Dr. Rifkin's letter seems to contain frank misinterpretations of our position. We supposedly argued that multidimensional ratings are as good as typological categories. We did not; we only pointed out that the issue is far from settled and that conceptual preference dictated choice. He complains that *DSM-III* is not empirical enough and thus implies we argued that it is too empirical. We never did. Obviously, the more data that can be accrued in support of diagnostic entities, the better. We argued that classical empiricism is not the best means for achieving this more mature scientific status. The terms "empiricism" and "empirical" are not interchangeable, and while we criticize the former, we are certainly not opposed to the latter.

Dr. Rifkin argues that empirical usefulness is the main point to be considered and that this apparent variant of pragmatism renders the theory-laden nature of scientific seeing unimportant. Does Dr. Rifkin consider the matter irrelevant merely because he is comfortable with the underlying philosophy he has selected and thus considers things solved? Does a pragmatic approach really settle matters, or do we need to examine its underlying assumptions also?

Ultimately, pragmatism is scientifically impractical. Suppose we use treatment response as one "test" for the usefulness or the definition of our diagnostic entities. Socioeconomic status is often a better predictor of treatment outcome than current diagnostic categories. Thus, I suppose we should have a diagnostic category for low socioeconomic status. We of course do not, because not just any subdivision will do, and the manner of categorization must have some conceptual, scientifically meaningful (theoretical) appeal. The limits of treatment response as a test of categorization are also well known; many treatment responses are nonspecific. More important, reasoning backward from results to cause or category is faulty logic. If someone is Lawrence Welk, he plays the accordion, but if I see my son playing the accordion, I would not conclude that he is Mr. Welk.

The pragmatic and the theoretical resist clear division. What could be more basic or abstract or theoretical than mathematics, and yet what system of thought has had more applied uses? Let us not become blinded or fragmented by false dichotomies. With rare exception, science becomes a powerful tool for understanding, prediction, and application when theories attain a high degree of verisimilitude. Thus, whether one's interest is "purely" basic or "purely" applied, probably the most important question to ask is whether the system "carves nature at the joints."

Dr. Rifkin's challenge is a gratuitous one. We do not claim the superiority of a multidimensional system and thus need not defend it. I also cannot resist pointing out that multidimensional systems are much more suited to the pragmatic classification approach than Dr. Rifkin seems to endorse. Further, is Dr. Rifkin saying that one should not criticize unless one has a better alternative? If so, perhaps medicine should stop diagnosing any untreatable disorders.

The issue is not whether Drs. Faust and Miner can do better, but what it will take, as a field, to do better with classification. Method is secondary to our current limits. Lack of scientific knowledge is primary. Debate should focus on how we can best advance our scientific knowledge. We argue that it is not by embracing a narrow variant of empiricism on which we risk all.

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Time and the Meaning of Human Experience

SIR: The article "Systems and the Structuring of Meaning: Contributions to a Biopsychosocial Medicine" by Michael Alan Schwartz, M.D., and Osborne P. Wiggins, Ph.D. (1), albeit enlightening and comprehensive, seems to have left out the "fourth dimension." Time certainly is another principle that organizes the interaction between the individual and his or her environment, besides being the structure that provides for measures of reduction of complexity and that imparts direction to all the ongoing processes within open systems.

Straddling the biological (subatomic to nervous system) and personal/environmental (dyadic through cosmic) systems within which every individual human existence simultaneously operates, time is a crucial regulator of the psychobiological functioning of individuals, e.g., through universal (bio)rhythms (2, 3) and through the psychosocial interaction of individuals coordinating their joint ventures, especially in Western civilization (3).

More than two decades ago, Ernest Becker (4), while musing on the meaning of human experience, pointed out that "man is the only 'time-binding' animal" capable of transcending "subjective time" and abiding by measured, "sequential time." "Behavioral time" would be "the creative merger of inner and outer worlds—the process of integrating measured time-spans into the organism" (4, p. 29), locking into the unique set of memories all of the individual's past experience. Individual memory is what personal identity is all about, and it confers much of the meaning to both present and future experiences.

More pertinent for psychiatry, "psychotherapy is an interpersonal process which is time-linked" (5, p. 216). Failure to share the same (sequential) time perspective, and thus lack of

future orientation, is a recognized obstacle to traditional psychotherapy with Amerindians (6).

Measured time has become such an integral part of our "clockbound culture" that we welcome with incredulity the historical evidence of its invention, on the heels of polyphonic music, only in the late Middle Ages (3). From the time of Plato and Aristotle to that of Copernicus and Kepler, the concept of time was welded to motion and space, as it still is in the preabstract stages of individual cognitive development. Time as a mental construct and an independent variable, or sovereign dimension, was not discovered until Galileo and Isaac Newton in the seventeenth century, we are told (3).

On the other hand, deciphering the "biological clocks" and circadian rhythms (2) that have been running all living organisms' schedules forever not only is vital to the inquiry into the natural history of mental illness but promises to help fine-tune our psychotherapeutic and chemotherapeutic interventions.

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Drs. Schwartz and Wiggins Reply

SIR: Dr. Kubacki's comments correctly emphasize the role of time in a comprehensive biopsychosocial (systems) approach to medical practice. We did not concern ourselves with time in our essay simply because we chose to focus on other issues, but we are pleased to respond to Dr. Kubacki's remarks.

In our opinion, Niklas Luhmann (1, 2) and other European thinkers (3–5) have made important contributions to our comprehension of time. These investigators have taken us far beyond prevailing modern views of time as a succession of "now-points." Such views confuse the mere measurement of time with time itself.

Time is of fundamental importance to Luhmann's systems theory in several ways. Because of their largeness, complex systems cannot relate all of their parts together simultaneously. Such relationships can occur, therefore, only over time: relationships among the system's components must be temporalized. Complex systems use time to select more relationships sequentially than could ever be selected simultaneously. Time thus makes possible, in Luhmann's words, "an extension of choice."

For psychological and social systems, any event occurs within a temporal horizon of other possible events that are related to one another through meaning structures. In such systems a "punctual present" in which the future continuously becomes the past can coexist with a "lasting present" in which "one can delay, and, if necessary, work out what ought to be" (2, p. 133). Within this lasting present, time remains reversible: what was negated through an earlier act of selection can for a while be reactualized. Once events pass beyond this lasting present, however, they become irreversible and can be regained only in memory.

Obviously, these matters remain too difficult to present without extensive discussion and examples. They have been well developed in an essay by John Bednarz, Ph.D. With Dr. Bednarz's permission, we shall be glad to send this essay to anyone on request.

Certainly, appreciation of human time is of great interest to psychiatrists concerned with a wide array of subjects, including the psychopathology of time as expressed in numerous psychiatric disorders; time perception as related to circadian rhythms and biological blocks; the relationship between time, conscious experience, and memory; and time and the human life cycle.

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Outpatient Civil Commitment

SIR: Two articles (1, 2) and an accompanying editorial (3) indicated that outpatient commitment has substantial clinical benefits, but they appeared to neglect discussion of potentially deleterious operational, economic, and legal consequences.

The enforcement of an outpatient civil commitment system would be difficult at best. Viewing the operation of such a system as analogous to the existing parole and probation system in the criminal justice area would predicate a similar operational deficiency in the civil area. Given the amount of resources needed to operate the parole system effectively, considerable financial resources would also be needed to operate an outpatient commitment system effectively.

As for economic issues, it is unclear whether cost savings would be derived from outpatient treatment, as opposed to more structured treatment, for many seriously disturbed psychiatric patients. Our recent history of mental health "advances," such as the use of neuroleptics, deinstitutionalization, and the community mental health movement, has met with a decreasing allocation of resources for mental health needs. Given this history, local governments would be likely to use any hint of clinical success with outpatient commitment as a rationale for decreasing the already minimal funding for outpatient services.

Legal quagmires also lie in wait for outpatient commitment. The issue of committed outpatients' right to refuse

pharmacotherapy has yet to be addressed. Increased civil liability for patients' acts seems likely, given recent unpredictable legal decisions (4) and the public's anticipated perception that the behavior of committed outpatients should be the responsibility of the treating psychiatrist. Like inpatient commitments, the overwhelming majority of outpatient commitments will be administered by public sector psychiatrists. Public sector psychiatrists, especially in community mental health centers, are generally overburdened and relegated to minor clinical and administrative roles (5), yet they are generally held to be ultimately responsible for patient care and would also likely be held ultimately responsible for committed outpatients. Therefore, to have sufficient psychiatric involvement to implement successful outpatient commitment, additional psychiatrists would have to be recruited. This is an unlikely eventuality in these days of fiscal restraint. In addition, legal conflicts would frequently arise among patients, their legal advocates, and psychiatrists, leading to a decrease in the time psychiatrists could devote to direct patient care. Again, additional psychiatric manpower would be needed, but this possibility, as I have said, is remote.

Before enthusiastically supporting outpatient commitment, it would seem prudent for psychiatrists to exercise caution and examine critically the potential operational, economic, and legal consequences of such a system, not merely its superficial clinical benefits, lest we open Pandora's box with our therapeutic zeal.

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GREGORY B. LEONG, M.D.
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Dr. Bursten Replies

SIR: Dr. Leong incorrectly describes my paper as indicating that outpatient commitment results in substantial clinical benefits. On the contrary, the whole point of my paper was to show that such benefits have not been demonstrated. With the exception of this inaccuracy, I feel that Dr. Leong raises some very important points—points that are entirely consistent with the thrust of the paper.

BEN BURSTEN, M.D.
Oak Ridge, Tenn.

Dr. Geller Replies

SIR: While not responsive to the content of the two articles and the editorial he criticizes for being neglectful of certain aspects of outpatient commitment, Dr. Leong's remarks deserve comment. For a more complete discussion of the "operational, economic, and legal consequences" of outpatient commitment that Dr. Leong seeks, the reader is referred to recent publications on these points (1–3).

Dr. Leong indicates that the economic savings from outpatient commitment, as compared to inpatient commitment, are unclear. I agree; empirical studies are required to clarify this. However, to caution against outpatient commitment because its success might further decrease allocations for mental health services and, specifically, diminish funding for inpatient services is unwarranted. There is no negative correlation between successes in mental health treatment and expenditures; despite a major shift in the loci of care and treatment of the chronically mentally ill from state hospitals to community settings over the last 30 years, state hospitals continue to receive more than 65% of state mental health agency expenditures, and there is little correlation between the quality of a state's public sector psychiatric service system and the state's per capita expenditure for mental health (4). If we follow Dr. Leong's argument to its logical conclusion, we should refrain from financing research on the etiology and definitive treatment of schizophrenia, since such discoveries will lead to lessening of funding for mental health services.

The legal quagmires of outpatient commitment are many, and Dr. Leong points out some of them. The major one will be liability for committed patients' acts, and this needs to be statutorily addressed by the states. The issue of the right of committed outpatients to refuse pharmacotherapy has been addressed in some states. In Massachusetts, for example, where a state judicial proceeding rather than a state statute produces involuntary community treatment, patients are being involuntarily treated with neuroleptic medication in the community.

I concur with Dr. Leong's belief that the already overburdened public sector psychiatrist in the community mental health center (CMHC) will be a central figure in carrying out outpatient commitment orders. That this will increase rather than decrease his or her clinical burden is not clear and requires empirical investigation. Study is also required to determine whether outpatient commitment will be a repetitive, litigious process, pulling the psychiatrist from direct patient care, rather than a procedure that will make relationships and authority clear for a defined period, decrease recidivism and the consequent commitment hearings, and lessen "negotiations" in front of patients with legal advocates, so that the psychiatrist is *more* available for direct patient care. Finally, Dr. Leong's implication that the already disempowered CMHC psychiatrist might well suffer further diminution in his or her status flies in the face of his concern that the psychiatrist will be central to the process of outpatient commitment.

There are many issues that need to be addressed before one embraces outpatient commitment. On that Dr. Leong and I agree. In addition to exercising caution and examining critically, however, psychiatrists should be proactive, so that state statutes governing outpatient commitment are those we can live with.

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What About the Bicameral Mind?

SIR: I found the review article "Hallucinations: Theoretical and Clinical Overview" by Ghazi Asaad, M.D., and Bruce Shapiro, M.D. (1), to be basically quite informative and useful. However, in the theoretical overview, they did seem to leave out one major theoretical perspective, as controversial as it may be. That perspective is the "bicameral mind," as proposed by Julian Jaynes (2). Using an evolutionary perspective, Jaynes proposed that hallucinations were a normal phenomenon—in fact, the usual mode of thinking—from about 9000 B.C. to about 1500 B.C. The bicameral mind, with its controlling voices, evolved as a final stage in the evolution of language. Presumably, the dominance of a right temporal area corresponded to this development in our thinking, which, among other things, allowed agriculture to begin. The end of the dominance of the bicameral mind, and the beginning of modern consciousness, came about through the advent of writing, the chaos from natural and man-made disasters, and the differences in clashing cultures. Contemporary "regressions" to bicamerality may include schizophrenia, as well as religious prophecy, possession states, hypnosis, and other phenomena such as poetry and music. I wonder what the authors think of this theory.

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H. STEVEN MOFFIC, M.D.
Houston, Tex.

Drs. Asaad and Shapiro Reply

SIR: We thank Dr. Moffic for his stimulating letter regarding Julian Jaynes's theoretical perspective of the bicameral mind as it relates to our article. Indeed, we had not included Jaynes's hypothetical construct in our review.

The bicameral mind hypothesis is fascinating in its eclectic and interdisciplinary attempt to explain the phenomena of hallucinations. As Dr. Moffic suggests, it lies outside the mainstream of contemporary psychiatric thought. We did include a discussion of the work of Penfield (1), upon which much of the neurophysiologic and neuroanatomic arguments made by Jaynes in his chapter "The Double Brain" rests (2). The difficulty which we find with Jaynes's hypothesis is that the conclusions he draws have a questionable basis in neuropsychiatric fact. It is difficult to accept the presence of a God-like faculty that rests in the right temporal area, commanding ancient man as well as the modern schizophrenic in a voice perceived as that of the deity. In addition, in the face of the age-old question of the association (or differences) between creativity and madness, it should also, in our opinion, still remain difficult to apply such simplistic views to explain artistic inspirations, hypnosis, or other altered perceptions, as mentioned in Dr. Moffic's letter. Indeed, if Jaynes's hypothesis were to coincide more accurately with anatomic fact, the right temporal area in question would more likely coincide with Broca's expressive area—a notion that does not conveniently fit Jaynes's theoretical constructs. In addition, it is now well known that lesions of the right-sided areas corresponding to Broca's or Wernicke's areas result in expressive or receptive aprosodias, as illustrated recently by Fricchione and colleagues (3); these areas would thus seem more related to the negative symptoms of schizophrenia (such as restricted affect) than to the positive hallucinatory symptoms. Jaynes's concept of the bicameral mind emphasizes what he feels are the auditory and religious essences of hallucinations, again oversimplifying the diverse and complex nature of hallucinatory phenomena to which we alluded in our review. Most clinicians who have worked with psychiatric patients would realize how simplistic an explanation the bicameral mind hypothesis is when faced with the myriad forms of hallucinations.

Julian Jaynes's hypothesis makes for interesting reading and stimulates much thought in the receptive reader. It does not, however, adequately explain one of the central mysteries of madness: hallucinations.

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GHAZI ASAAD, M.D.
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Hallucinations as Conversion Symptoms

SIR: The otherwise comprehensive review of hallucinations by Drs. Asaad and Shapiro (1) did not include the occasional presentation of hallucinations that fulfill all of the criteria for the diagnosis of conversion reactions (2, 3). This conceptualization is of obvious importance for appropriate treatment as another nonpsychotic state associated with hallucinations.

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Drs. Asaad and Shapiro Reply

SIR: We thank Dr. McKegney for his letter about our article, and we understand his concern regarding what he feels may be the omission of conversion reactions as possible "nonpsychotic state(s) associated with hallucinations."

We are familiar with the longstanding literature on what have traditionally been described as hallucinations occurring in hysterical disorders, and we feel that there are a few points which deserve some clarification in this area. Dr. McKegney's two case descriptions in his 1967 article (his reference 1) more likely fit the criteria for pseudohallucinations (i.e., hallucinations accompanied by some insight) than for hallucinations in the sense of classical psychotic symptoms. In a study by Goodwin et al. (1) of 117 hallucinating patients, 71% of the hysterical patients felt that the hallucinations "may have been due to [their] imagination." In that same report it was noted that 12% of the hysterical patients hallucinated. Clearly hallucination-like phenomena are common in the hysterical spectrum of disorders. We raise this question, though: are these mostly hallucinations (as seen in schizophrenic disorders or major depressive disorders with psychotic features), or are these more likely pseudohallucinations? We suspect that they may commonly be the latter, not hallucinations in the classic sense. They may, alternatively, reflect some aspect of altered states of consciousness or dissociative states to which we alluded in our article. More likely still, we might recommend resurrection of the now outdated (but perhaps quite useful) category of hysterical psychosis. In addition, it is important not to overlook the rather common transient psychotic (or micropsychotic) episodes found in patients with borderline personality disorder. We know well that the hysteroid borderline patient is quite capable of presenting with a variety of psychotic symptoms, including hallucinations and pseudohallucinations.

We hope that Dr. McKegney's letter will serve to underscore the need for the clinician to think in terms of a wide differential diagnostic range when presented with a hallucinating patient. As we noted in our article, a hallucination does not a schizophrenic make.

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Correction

In the article "Prediction of Postdexamethasone Cortisol Levels by Serum Sodium Levels in Patients With Major Depression" (January 1986 issue, pp. 81–84) by Gary D. Tollefson, M.D., Ph.D., et al., there was an error in the final paragraph on p. 83. The sentence "For classification purposes, when a pre-DST sodium level is less than or equal to 140 meq/liter, a DST will reveal *nonsuppression*" should instead say ". . . a DST will reveal *suppression*." Also, in table 1, potassium at 8:00 a.m. should be 4.176±0.33 rather than 4.176±3.30.

The staff regrets these errors.

Reprints of Letters to the Editor are not available.

Position Statement on Psychoactive Substance Use and Dependence: Update on Marijuana and Cocaine

This statement is an adjunct to the position statement on substance abuse published in the June 1981 issue of the American Journal of Psychiatry, *which emphasizes diagnosis and treatment. It replaces the position statement on marijuana laws published in the May 1979 issue of the* American Journal of Psychiatry. *The statement was prepared by the Committee on Drug Abuse[a] of the Council on Psychiatric Services and was approved by the Assembly in November 1986 and by the Board of Trustees in December 1986.*

The misuse of psychoactive substances is the nation's foremost public health challenge. The use and abuse of alcohol, cigarettes, illicit drugs (heroin, cocaine, marijuana, etc.), and licit drugs (sedatives and tranquilizers) are by far the largest cause of preventable and premature illness, disability, and death in our society. The annual economic cost of alcohol and drug abuse has been estimated to be $136 billion, over four times that of cancer and nearly a third greater than that of cardiovascular disease (1). Illicit drug use has increased so rapidly over the past 25 years that it may be difficult for someone over age 50 to comprehend the extent to which drugs have permeated our society. Experience with illicit psychoactive drugs was restricted to 2% or less of the population in most areas of the country in the early 1960s (2). In contrast, the 1982 household survey (3) found that almost a third of the household population in the United States age 12 and older had had some experience with illicit drugs. Almost 60 million household residents had tried marijuana, and an estimated 20 million were current users. In 1982, it was estimated (4) that over 20 million had tried cocaine and over 4 million were current users. The prevalence of cocaine use and abuse has increased dramatically in the ensuing 4 years (4).

Illicit drug use is most prevalent in young adults. Typically, children begin experimenting with drugs of abuse by trying alcohol and cigarettes in early adolescence. By the time they complete secondary school, they have established attitudes toward drugs and patterns of use that will carry them through much of their lives. Most adults addicted to nicotine through smoking cigarettes established regular smoking in their teens. Adult users of cocaine and opiates generally began drug use in adolescence and may have been heavy marijuana users (5). In addition to exposing themselves to the risks of drug use (automobile accidents, overdose, or impaired physical, emotional, and psychological development), adolescents are establishing attitudes toward and actual patterns of use that have profound long-term consequences on health. By the time they graduate, more than half (54%) of high school seniors have tried marijuana and a fourth (26%) are current users. Cocaine use tends to begin a few years later than marijuana use, and heavy marijuana use is an important risk factor for cocaine use. Nevertheless, cocaine use now is increasing among our high school population. In the 1985 national survey of high school seniors (6), it was found that 17% had tried cocaine and almost 7% were current users.

In addition to statistics on the prevalence of use, there are now data from National Institute of Mental Health (NIMH) catchment area studies (7) on the lifetime prevalence of substance abuse disorders, which was found to vary from 15.0% to 18.1% among the three sites reported. These rates were significantly higher than the lifetime prevalence of any other group of disorders (except for phobic disorders at one site).

SOCIAL CONSEQUENCES OF USE OF MARIJUANA AND OTHER DRUGS

Young people may use drugs in an attempt to alleviate problematic family relationships. Over the short term, drugs may allow the young person temporarily to ignore intrafamilial strife, including developmental adjustments between child and parents and among siblings. Regular or heavy drug use undermines the adolescent's ability to work through these problems with other family members, thereby exacerbating family problems over the long term. The heavy drug user may withdraw socially from other family members, refuse to consider their needs and concerns, and put his or her own needs above those of the family. Theft from other family members (to obtain drugs) and lying (to hide drug use) undermine the trust necessary for coexistence within the family. Angry outbursts, property destruction, and intrafamily violence can ensue. Alienation of the drug user from the family, once present, is difficult to repair (8). Adult substance abusers also exert powerful effects on their families. Families react variably but often go through stages of denial, overprotection, personal mental illness, and family disruption. The effects on children in such families have been so profound that a national movement, the Adult Children of Alcoholics, has recently emerged to provide support and understanding (9–11).

Heavy drug use can precipitate financial problems in two ways. First, drugs themselves cost money; drug expenses are proportional to the cost of the drug, frequency of use, and dose consumed. Such costs mount as tolerance develops, habitual use becomes established, and larger amounts of drug are consumed more often. A second source of financial problems is unemployment or job loss. Early drug use may seem to facilitate work by alleviating fatigue or boredom or helping the user tolerate work-related stresses. Eventually, continued drug use undermines the person's energy, ambition, concentration, problem-solving abilities, performance, productivity, and social skills in dealing with co-workers and supervisors. Drug-induced paranoia, if present, further exaggerates interpersonal dissensions. In addition to individual financial loss, theft and unpaid loans from other family members can cause financial difficulties for the entire family.

The heavy drug user may resort to criminality to financially support the drug habit. Theft and illicit drug selling are the most

[a]The Committee on Drug Abuse includes Edward Kaufman, M.D. (chairperson), Edward Khantzian, M.D., Joseph Westermeyer, M.D., Dorynne Czechowicz, M.D. (consultant), Steven Mirin, M.D. (consultant), and Roger Meyer, M.D. (former member).

common illegal activities, but prostitution, robbery, and drug smuggling also occur. Easy money from criminal behavior impedes later rehabilitation, since the youthful person has been learning criminality rather than a licit occupation during this critical development period. Learning a job skill or profession requires hard work, willingness to make a commitment and risk failure, and learning responsibility, tasks not easily accomplished. Frustration, anxiety, and fear result to a greater or lesser extent, feelings that marijuana, cocaine, and other drugs can alleviate temporarily. Continued drug use undermines the persistence and industriousness needed to succeed at this developmental task. Drug intoxication and, later, withdrawal, impair the ability to concentrate, synthesize, and organize material, learn new material, apply general principles to specific problems, exert judgment in complex tasks and situations, and make timely decisions (12).

In developing friendships and, later, intimacy with persons of the opposite sex, most youthful persons experience anxiety, embarrassment, and fear of rejection. They may believe that drugs can relieve these aversive feelings as well as alleviate premature ejaculation (in males) and vaginismus (in females). However, prolonged heavy use can reverse these temporary gains in sexual performance, leading to anhedonia, amenorrhea, impotence, and rejection by a sexual partner (13). The lack of judgment seen in young drug and alcohol users often results in teenage pregnancy.

Adolescence is the time to acquire hobbies, sports, and other avocations that may last decades, even a lifetime (14). By and large, drug use does not enhance these activities. Drug use may in fact lead to abandonment of these pursuits and may intensify social isolation. Instead, the drug user pursues activities that focus on the drug use experience and that tend to be banal and boring if done without drug use. Thus, without drugs, the chronic user may be bored and at a loss for stimulating and rewarding activities. Recreational pastimes usually require a period of learning and acquiring skills, another lengthy process that is abandoned with drug use. Drug use during activities involving rapid psychomotor coordination, speed, and judgment (e.g., driving a car or motor boat, water or snow skiing) places the intoxicated person at risk of harming self or others.

In the process of becoming an adult, an adolescent learns to accept responsibility and cope with adversity. Maturation demands a focus outside oneself, task orientation, and the ability to delay gratification for a time. This personality development is impaired by the use of drugs, which furthers an egocentric and present-oriented attitude. If regular drug use began early in adolescence and was continued over several years, the recovering abuser often has the personality characteristics and maturation level of a much younger person (15). It is important to note that alcohol and cigarettes are "gateways," predecessors of marijuana use, which is in turn a predecessor of other drug use and abuse (16).

CONSEQUENCES OF MARIJUANA USE

General Medical Consequences

Two distinguished independent scientific groups separately have reported on marijuana in the past 6 years. The Institute of Medicine, National Academy of Sciences, prepared a report on marijuana and health that was published in 1982 (17). The Addiction Research Center, World Health Organization, prepared a report on the Conference of Adverse Health and Behavioral Consequences of Cannabis, which was published in 1981 (18). Both reports concluded that cannabis has both known and suspected health hazards that should be of serious national concern.

The health consequences of chronic marijuana use depend to some extent on the frequency, duration, and intensity of use, the age at which use begins, and biopsychosocial characteristics of the user, which may contribute to risk in still unspecified ways. For example, not all individuals who smoke tobacco cigarettes will go on to develop carcinoma of the lung, but the risk of this disorder is much greater among smokers, and the relative risk increases with the intensity, frequency, and chronicity of use.

Since the two aforementioned studies were published, further evidence of the harmful effects of marijuana has been established. In particular, the clearest evidence for harmful changes in physical health involves the pulmonary system (19–22 and a December 1979 report of the AMA Council on Scientific Affairs). Bronchitis and related inflammatory changes have been shown repeatedly. More recently, it has been shown that marijuana smoking causes a significant reduction in the gas-diffusing capacity of the lung. Moreover, there is considerable evidence to suggest that long-term use, like tobacco smoking, may lead to pulmonary cancer. Indeed, marijuana has up to 50% more aryl hydrocarbons in its smoke than tobacco, and high levels of these are associated with susceptibility to bronchogenic carcinoma. Many marijuana smokers also smoke tobacco, and it is postulated that the combined effects of smoking both substances may substantially increase the risk of cancer. Most important are the profound acute and chronic psychosocial, cognitive, and behavioral effects associated with marijuana use by youth. Acute toxicity is accompanied by negative effects on learning and memory, as well as psychomotor impairment. The typical effects of cannabis resemble a transient acute brain syndrome; they include deficits in attention span, concentration ability, short-term memory, information processing, and the performance of complex perceptual motor tasks. Thus, accidental injury to persons driving motor vehicles, piloting airplanes, or operating heavy machinery while intoxicated with marijuana is of special concern.

Even when marijuana use is discontinued, the memory loss continues for 3 to 6 months. This particularly affects adolescents who have been having difficulties in school. This consequent negative reinforcement leads them to return to marijuana use.

Specific Psychiatric Concerns

Psychiatrists have described three general complications associated with cannabis: acute adverse reactions, flashbacks, and prolonged reactions. Acute reactions are characterized by errors in judgment and confusion, which may be followed by an amnesic period. These are dose related and fall within the general category of deliria (23, 24). Anxiety may progress to acute pain reaction with overwhelming anxiety and a fear of losing control in response to drug-induced symptoms. Factors related to setting and/or personality may lead to severe anxiety.

Flashbacks refer to brief, spontaneous recurrences of mental states experienced during marijuana intoxication that occur sometime after the last drug use. At this writing, the exact mechanism for flashbacks is uncertain.

Prolonged reactions secondary to marijuana use include psychotic and nonpsychotic reactions. Marijuana smoking may trigger a schizophrenic reaction in vulnerable individuals. Descriptions of long-lasting cannabis-induced psychoses appear mainly in medical journals in Asia and North Africa, where individuals may use cannabis at substantially higher doses than in the United States. Descriptions of cannabis psychoses vary by culture, and most reports suggest a persistent delirium, which includes bizarre behavior and the potential for violence and panic feelings in the absence of a "typical" schizophrenia-like psychotic state. There is fairly general agreement that persons suffering from marijuana psychosis do not develop psychotic thoughts or symptoms characteristic of schizophrenia. Most reports describe cannabis psychosis as lasting 1–6 weeks among very heavy users of high doses of cannabis. However, some reports describe longer-lasting marijuana psychoses in which the psychotic episodes do not clear in the usual time but persist in residual form. Repeated intoxications may result in recurrent psychotic episodes. There has been a problem in relating marijuana psychosis to the experience in Western countries because of differences in smoking patterns in the East and the West, the difficulty of translating the psychiatric symptom picture from one body of literature and culture into another, and the impossibility of generalizing from cases that come to psychiatric attention to the overall marijuana-using population.

Nonpsychotic prolonged adverse reactions have also been described. Chronic anxiety states, depressive symptoms, and changes in life style (including an "amotivational syndrome") have been linked to chronic marijuana use by a number of observers. The amotivational syndrome includes apathy, loss of effectiveness, and diminished capacity or willingness to carry out complex long-term

plans, endure frustration, concentrate for long periods, follow routines, or successfully master new materials. Verbal facility often is impaired both in speaking and in writing. Such individuals experience greater introversion, become totally involved with the present at the expense of future goals, and demonstrate a strong tendency toward regressive, childlike, magical thinking. It remains unclear whether those who are attracted to heavy marijuana use already were inclined toward an amotivational syndrome, of which the marijuana use was symptomatic, or whether the amotivational syndrome developed as a consequence of the chronic marijuana use. What is clear is that chronic marijuana smokers who develop amotivational patterns of behavior need to stop marijuana use if they are to be rehabilitated.

Finally, the question of marijuana's dependence-producing capability is raised frequently. Laboratory animals do not self-administer Δ^9-tetrahydrocannabinol as they do opioids, sedative hypnotic drugs, alcohol, and stimulants. Nevertheless, compulsive patterns of cannabis consumption do develop in human beings, and heavy use of marijuana in humans is associated with the development of a dependence syndrome. Moreover, heavy users of marijuana appear to be at substantially greater risk for other forms of drug abuse than persons who do not use marijuana. Finally, the long persistence of cannabinoids in the body after ingestion (up to 9 days after a single dose) raises the additional prospect of toxicity due to accumulation of the drug and its metabolites in the brain and other lipid-containing organs.

CONSEQUENCES OF COCAINE USE

The growing popularity of cocaine, as a drug of both use and abuse, is testimony of the willingness of human beings to consume psychoactive substances without regard to their effects on the brain or other body organs.

The adverse effects of cocaine on health may be divided into the general medical, specifically psychiatric, and social sequelae of acute and chronic use. The probability that adverse effects will occur is, in turn, related to factors such as dose, route of administration, and frequency and duration of use. Changing routes of cocaine administration (such as "free basing" or using "crack") increases the severity of health consequences. Frequent administration, even over short periods of time, leads to the accumulation of cocaine in plasma and presumably in brain tissue and increases the risk of adverse medical and psychiatric sequelae. Cocaine rapidly depletes endogenous neurotransmitters, leaving the user in a depressed state. Individual tolerance and vulnerability to the physical and psychological effects of the drug also play a role.

General Medical Consequences

Some sequalae of cocaine use stem from the drug's local anesthetic properties, its direct effects on small capillaries, and its ability to stimulate sympathetic nervous system activity. Other medical complications are the indirect result of the drug-using life style.

Until the upsurge of smoking crack cocaine, 80% of all cocaine use was by nasal inhalation (snorting). The direct effects of the drug on mucous membranes are responsible for a number of medical complications. These include rhinitis, erosion of the mucous membranes, and in severe cases, perforation of the nasal septum (25). Intravenous cocaine use, favored by some for the rapidity of onset and intensity of drug effects, is associated with all of the complications that one might expect with any type of unregulated intravenous drug use. These include skin abscess, thrombophlebitis, septicemia, hepatitis B, acquired immune deficiency syndrome (AIDS), and tetanus (26). Smoking the basified extract of cocaine (free basing or crack smoking) delivers the drug into the pulmonary capillary bed, where it is rapidly absorbed and results in a dramatically intense effect and a more rapid onset of addiction. Free basing and crack smoking have been associated with the development of chronic bronchitis and impairment in pulmonary diffusing capacity (27).

Cocaine's ability to stimulate the sympathetic nervous system may result in elevated heart rate and increased susceptibility to premature ventricular beats and, in some vulnerable individuals, ventricular fibrillation, respiratory arrest, and death (28). Acute elevations of blood pressure, with headache and the potential for cerebral hemorrhage, also have been described (29). Increased body temperature due to failure of the brain mechanisms controlling heat regulation, coupled with vasoconstriction and hyperactivity, has led to some deaths from hyperthermia (30).

Another untoward effect of cocaine is the development of status epilepticus. This may occur either as an acute response to high-dose use or as a result of a sensitivity to cocaine developed during chronic administration. The latter may be due to a so-called "kindling" phenomenon, in which brain neurons become increasingly sensitized to the effects of cocaine and fire in response to even relatively low doses of the drug (30).

All of the adverse medical complications of cocaine use are far more likely after acute administration of large doses. In many instances overdose is unintentional, since the user has little knowledge of the purity or even the amount of the drug consumed. Overdose deaths have occurred after the first use in apparently healthy individuals with no preexisting illness. In addition, repetitive use is associated with increasing sensitivity in some of the excitatory effects of cocaine. Finally, a small number of individuals suffer from a congenital lack of the enzyme pseudocholinesterase and thus are unable to metabolize the drug. In these individuals, even small doses can produce dramatic effects. The medical complications of cocaine use are more likely to occur in persons with preexisting heart or respiratory disease, hypertension, seizure disorders, or compromised immune function and in those who are taking other drugs whose effects are potentiated by cocaine.

Specific Psychiatric Complications

The acute subjective response to cocaine is characterized by euphoria, insomnia, increased energy, enhanced mental acuity and alertness, and an increase in sensory awareness. However, some individuals become hyperexcitable, while others, particularly those with underlying depressive disorders, experience dysphoria. Anxiety, concentration difficulties, decreased attention span, and memory problems also have been reported after use of cocaine. In individuals with underlying panic disorder, the drug can precipitate panic attacks. Some cocaine users may misperceive reality and/or experience auditory, visual, and tactile hallucinations. Flight of ideas, distractibility, pressured speech, restlessness, impulsivity, and poor judgment are common. Paranoia and delusions of persecution, coupled with profound irritability and grandiosity, may lead to assaultive and/or homicidal behavior by some cocaine abusers. These alterations in thinking, mood, and behavior may last a short time or, in certain vulnerable individuals, may persist long after the drug has been metabolized (31, 32).

Chronic cocaine use also is associated with untoward effects on psychological health. Several studies have demonstrated a direct relationship between cocaine dose, chronicity of use, and the development of cocaine-related psychopathology. Chronic cocaine users frequently complain of fatigue, headaches, impairment of recent memory, concentration difficulties, and sexual indifference. They also are more likely to develop a cocaine psychosis (described previously).

In some individuals the powerfully reinforcing effects of cocaine lead to increased frequency of use, escalation of dose, and the eventual development of psychological and physical dependence. The onset of dependence is particularly rapid with the use of crack. The primary reinforcing effects of the drug are probably mediated through the limbic system mechanisms responsible for the perception of pleasure—specifically, those neural circuits that use norepinephrine and dopamine as neurotransmitters. Other factors that contribute to the development of dependence include psychological variables, peer pressure, drug availability, and (perhaps) some sort of underlying biological vulnerability.

The tendency toward repetitive use is further enhanced by the occurrence of a cocaine withdrawal syndrome characterized by depression, lethargy, fatigue, feelings of guilt, anxiety, and feelings of helplessness, hopelessness, and worthlessness. In some individuals, particularly those with preexisting underlying depression, transient suicidal thoughts may emerge.

The cocaine withdrawal syndrome is particularly marked after chronic high-dose use. The signs and symptoms usually last 12–36 hours. In some individuals, however, the depression may last up to several weeks. To avoid withdrawal, some chronic users will self-administer the drug every 20–30 minutes. This pattern of use is more likely to be associated with the development of cocaine psychosis. The serious psychosocial consequences of cocaine use include loss of job and problems with one's family, friends, and finances.

In summary, both acute and chronic cocaine use are associated with adverse effects on health. In addition to medical and psychiatric sequelae, chronic cocaine use also is associated with the hazards of a drug-using life style. These include anorexia and associated weight loss, malnutrition and vitamin deficiencies, accidents, and a greater likelihood that one will be the perpetrator or victim of violence.

ROLE AND RESPONSIBILITY OF PSYCHIATRISTS

Psychiatrists should exercise a leadership role in drawing attention to the major public and mental health consequences of substance abuse in our society. Psychiatrists have a responsibility to educate the public about how ubiquitous drug abuse is and how it is both the cause and consequence of emotional problems. We must be aware that drug and alcohol abuse are often the primary problem among patients who present themselves to psychiatrists. Psychiatrists should take leadership responsibility in assuring that adequate training in substance abuse occurs at all levels of medical education and in influencing physician attitudes and behaviors as part of this training process. Psychiatrists also should interface with nonmedical care givers, such as educators, the clergy, counselors, and self-help groups, in imparting an understanding of the psychiatric implications of substance abuse. The psychiatrist's role in working with the family is essential.

Evidence has accumulated over the past decade that there is a significant association between psychopathology and substance abuse. In some instances, substance abuse has resulted from psychopathology and in other cases has been the cause of it. In either case, for most individuals regular reliance on drugs is incompatible with a life of meaningful relationships, productivity, and satisfaction. Substances of abuse are dangerous because they exert powerful deleterious effects on human emotions and behavior. Mind-altering drugs, including alcohol, create illusions that emotional distress can be avoided, that desired states or behaviors can be augmented, and that performance can be enhanced or improved. During adolescence, when particularly intense emotions, behaviors, and performance concerns loom large, this is a seductive and dangerous effect of drug use. However, these dangers also apply to other phases of life, when other developmental challenges are encountered and need to be mastered.

Psychiatrists should address the emotional and mental health needs of substance abusers. Psychiatrists should educate themselves and the public about how substance abuse affects the psychological and social functioning of individuals and their families and should take active roles in developing and establishing guidelines and protocols for the assessment and management of substance abuse problems. Psychiatrists should provide the public with information on the hazards of substance abuse through the media, public education campaigns, and contacts with other care providers and professional associations. Psychiatrists should take the initiative in developing guidelines and procedures for quality assurance and assessment of treatment outcome for substance abuse treatment programs. Finally, psychiatrists, through the American Psychiatric Association, should exercise an ongoing leadership role to assure nondiscriminatory reimbursement practices for substance abuse treatment services.

Each psychiatrist has a responsibility to understand and learn about substances of abuse; their psychoactive, toxic, and withdrawal effects; and how they interact with human emotions and behavior. Practicing psychiatrists must routinely obtain drug and alcohol histories, focusing not only on duration, amounts, and patterns of use but also on the effects that patients seek and obtain from the drugs they choose. Similarly, family histories of drug use and misuse patterns also should be obtained routinely. Psychiatrists should routinely consider whether their patients with psychiatric conditions suffer from concomitant substance abuse disorders and whether patients presenting with substance abuse disorders also might be suffering from coexistent treatable psychiatric problems. Psychiatrists should be cognizant of the life-threatening aspects of substance abuse as background for emphasizing the importance and necessity of obtaining control and abstinence at the onset of treatment. Accordingly, psychiatrists must learn how to use appropriate hospital and other residential treatment, support groups (e.g., Alcoholics Anonymous and Narcotics Anonymous), pharmacological treatment, and psychotherapeutic modalities (33).

Psychiatrists involved in the treatment of children and youth presenting with behavioral and emotional problems should be alert to the possibility that drug use may be a contributing factor. Close cooperation between psychiatrists, primary care providers, parents, and educators is needed to overcome the serious problems of alcohol and other drug abuse among our youth.

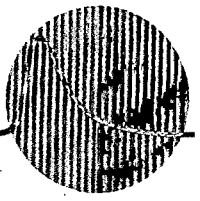
Finally, psychiatric practitioners are well suited to work with primary care providers in assessing and managing substance abuse patients in both outpatient and inpatient settings. They also are able to work with and interface with nonmedical caregivers, especially in consulting with self-help programs and drug counselors and helping them appreciate the mental health needs and psychiatric disabilities of their clients. The psychiatrist has a substantial contribution to offer in the management of the substance abuser. The psychiatrist can provide a dynamic understanding of the patient and can plan individualized multidisciplinary treatment and its implementation. It is the responsibility of the psychiatrist to emphasize the danger of drug use. To adopt a more neutral stance toward drug use by youth and refrain from warning of the dangers to mental health is to fail to fulfill an important public health responsibility of our profession.

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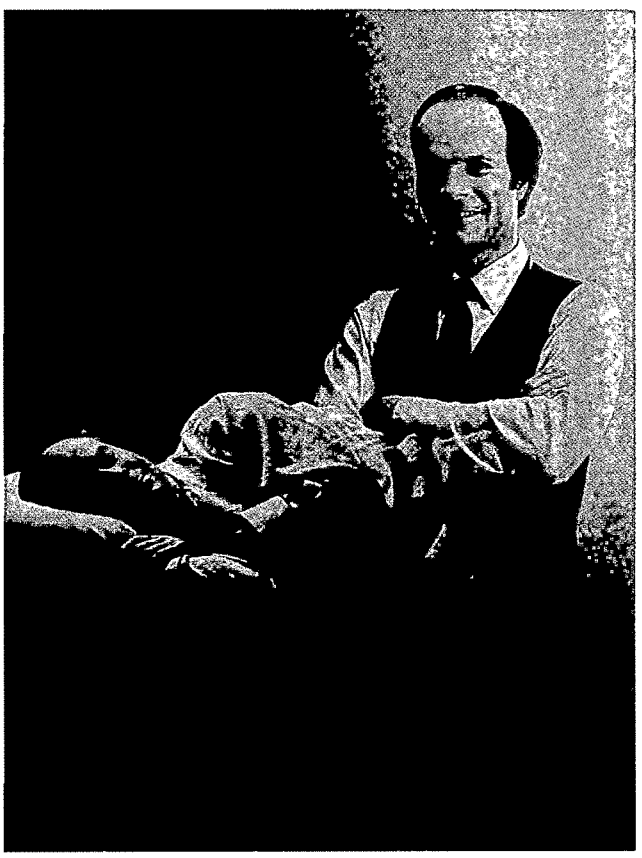
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INDICATIONS AND USAGE: HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS: Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS: Overdosage may occur at four times the maximum recommended therapeutic dose. Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS: *General:* In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. *Information for Patients:* Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing prescribed dosage, (e) possible worsening of sleep after discontinuing HALCION. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported, e.g., coadministration with either cimetidine or erythromycin reduced clearance, prolonged elimination half-life, and approximately doubled plasma levels of triazolam, hence increased clinical observation and consideration of dosage reduction may be appropriate. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. *Pregnancy:* Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. *Nursing Mothers:* Administration to nursing mothers is not recommended. *Pediatric Use:* Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS: During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g., drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE: *Controlled Substance:* HALCION Tablets are a Controlled Substance in Schedule IV. *Abuse and Dependence:* Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE: Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measure when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription. B-3-S

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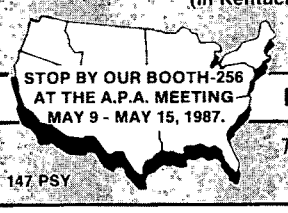
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THE COMMUNITY: This stable community of 70,000 has two colleges nearby and strong public and private school systems. There are numerous cultural and recreational opportunities. The closest medical school is in Shreveport, Louisiana 70 miles away. It is a three hour drive to Dallas and a two hour drive to Little Rock, Arkansas.

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ASENDIN®
amoxapine

ASENDIN® inhibits reuptake of norepinephrine and serotonin and also has dopamine-blocking activity which may be associated with neuroleptic side effects in some patients. Please see brief summary of prescribing information on adjacent page, especially **Warnings** *and* **Information for the Patient** *sections.*

ASENDIN® amoxapine

BRIEF SUMMARY
ASENDIN® amoxapine Tablets, 25 mg, 50 mg, 100 mg, 150 mg

CLINICAL PHARMACOLOGY: *ASENDIN is an antidepressant with a mild sedative component to its action. The mechanism of its clinical action in man is not well understood. In animals, amoxapine reduced the uptake of norepinephrine and serotonin and blocked the response of dopamine receptors to dopamine. Amoxapine is not a monoamine oxidase inhibitor.*

ASENDIN is absorbed rapidly and reaches peak blood levels approximately 90 minutes after ingestion. It is almost completely metabolized. The main route of excretion is the kidney. In vitro tests show that amoxapine binding to human serum is approximately 90%. In man, amoxapine serum concentration declines with a half-life of eight hours. However, the major metabolite, 8-hydroxyamoxapine, has a biologic half-life of 30 hours. Metabolites are excreted in the urine in conjugated form as glucuronides.

Clinical studies have demonstrated that ASENDIN has a more rapid onset of action than either amitriptyline or imipramine. The initial clinical effect may occur within four to seven days and occurs within 2 weeks in over 80% of responders.

INDICATIONS: *ASENDIN is indicated for relief of symptoms of depression in patients with neurotic or reactive depressive disorders as well as endogenous and psychotic depressions and depression accompanied by anxiety or agitation.*

CONTRAINDICATIONS: *Prior hypersensitivity to dibenzoxazepine compounds and in the acute recovery phase following myocardial infarction. Do not give concomitantly with monoamine oxidase inhibitors. Hyperpyretic crises, severe convulsions, and deaths have occurred in patients receiving tricyclic antidepressants and monoamine oxidase inhibitors simultaneously. Before replacing a monoamine oxidase inhibitor with ASENDIN® amoxapine, allow a minimum of 14 days to elapse, then initiate cautiously, with gradual increase in dosage until optimum response is achieved.*

WARNINGS: Tordive Dyskinesia: *Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may develop in patients treated with neuroleptic (ie, antipsychotic) drugs. (Amoxapine is not an antipsychotic, but it has substantive neuroleptic activity.) Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.*

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dosage of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treatment itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to neuroleptic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the sections on Information for Patients and Adverse Reactions.)

Use with caution in patients with history of urinary retention, angle-closure glaucoma, or increased intraocular pressure. Watch patients with cardiovascular disorders closely. Tricyclic antidepressants, particularly in high doses, can induce sinus tachycardia, changes in conduction time, and arrhythmias. Myocardial infarction and stroke have been reported with drugs of this class. Take extreme caution in patients with history of convulsive disorders or those with overt or latent seizure disorders.

PRECAUTIONS: General: *Because of inherent suicide potential, dispense to severely depressed patients the smallest suitable amount of the drug. Manic depressive patients may experience a shift to the manic phase; schizophrenic patients may develop increased symptoms of psychosis; patients with paranoid symptomatology may have such symptoms exaggerated, requiring reduction of dosage or addition of a major tranquilizer to the therapeutic regimen. Antidepressant drugs can cause skin rashes and/or "drug fever" in susceptible individuals. These allergic reactions may, in rare cases, be severe. They are more likely to occur during the first few days of treatment, but may also occur later. ASENDIN® amoxapine should be discontinued if rash and/or fever develop. Amoxapine possesses a degree of dopamine-blocking activity which may cause extrapyramidal symptoms in < 1% of patients. Rarely, symptoms indicative of tardive dyskinesia have been reported.* Information for the patient: *It is advised that all patients in whom chronic use of neuroleptic drugs is contemplated be given full information about the risk of tardive dyskinesia. Warn patients of possibility of drowsiness; performance of potentially hazardous tasks such as driving an automobile or operating machinery may be impaired.* Drug interactions: *See Contraindications regarding concurrent usage of tricyclic antidepressants and monoamine oxidase inhibitors. Paralytic ileus may occur when tricyclic antidepressants are taken in combination with anticholinergic drugs. ASENDIN may enhance response to alcohol and the effects of barbiturates and other CNS depressants. Serum levels of several tricyclic antidepressants have been reported to be significantly increased when cimetidine is administered concurrently. Although such an interaction has not been reported to date with ASENDIN, specific interaction studies have not been done, and the possibility should be considered.* Therapeutic interactions: *Concurrent administration with electroshock may increase hazards associated with such therapy.* Carcinogenesis, impairment of fertility: *In a 21-month toxicity study at three-dose levels in rats, pancreatic islet cell hyperplasia occurred with slightly increased incidence at doses 5-10 times the human dose. Pancreatic adenocarcinoma was detected in low incidence in the mid-dose group only, and may possibly have resulted from endocrine-mediated organ hyperfunction. The significance of these findings to man is not known. Treatment of male rats with 5-10 times the human dose resulted in a slight decrease in the number of fertile matings. Female rats receiving oral doses within the therapeutic range displayed a reversible increase in estrous cycle length.* Pregnancy. Pregnancy Category C: *Studies performed in mice, rats, and rabbits have demonstrated no evidence of teratogenic effect due to ASENDIN. Embryotoxicity was seen in rats and rabbits given oral doses approximating the human dose. Fetotoxic effects (intrauterine death, stillbirth, decreased birth weight) were seen in animals studied at oral doses 3-10 times the human dose. Decreased postnatal survival (between days 0-4) was demonstrated in the offspring of rats at 5-10 times the human dose. There are no adequate and well-controlled studies of pregnant women. ASENDIN should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.* Nursing mothers: *ASENDIN, like many other systemic drugs, is excreted in human milk. Because effects of the drug on infants are unknown, caution should be exercised when ASENDIN is administered to nursing women.* Pediatric use: *Safety and effectiveness in children below the age of 16 have not been established.*

ADVERSE REACTIONS: *Reported in Controlled Studies:* Incidence greater than 1%—*Most frequent were sedative and anticholinergic—drowsiness (14%), dry mouth (14%), constipation (12%), and blurred vision (7%).*

Less frequently reported reactions were: CNS and Neuromuscular—*anxiety, insomnia, restlessness, nervousness, palpitations, tremors, confusion, excitement, nightmares, ataxia, alterations in EEG patterns.* Allergic—*edema, skin rash.* Endocrine—*elevation of prolactin levels.* Gastrointestinal—*nausea.* Other—*dizziness, headache, fatigue, weakness, excessive appetite, increased perspiration.* Incidence less than 1%—Anticholinergic—*disturbances of accommodation, mydriasis, delayed micturition, urinary retention, nasal stuffiness.* Cardiovascular—*hypotension, hypertension, syncope, tachycardia.* Allergic—*drug fever, urticaria, photosensitization, pruritus, rarely, vasculitis, hepatitis.* CNS and Neuromuscular—*tingling, paresthesias of the extremities, tinnitus, disorientation, seizures, hypomania, numbness, incoordination, disturbed concentration, hyperthermia, extrapyramidal symptoms, including, rarely, tardive dyskinesia. Neuroleptic malignant syndrome has been reported.* Hematologic—*leukopenia, agranulocytosis.* Gastrointestinal—*epigastric distress, vomiting, flatulence, abdominal pain, peculiar taste, diarrhea.* Endocrine—*increased or decreased libido, impotence, menstrual irregularity, breast enlargement, and galactorrhea in the female, syndrome of inappropriate antidiuretic hormone secretion.* Other—*lacrimation, weight gain or loss, altered liver function.* Drug Relationship Unknown: *Reported rarely, but under circumstances where drug relationship was unknown:* Anticholinergic—*paralytic ileus.* Cardiovascular—*atrial arrhythmias (including atrial fibrillation), myocardial infarction, stroke, heart block.* CNS and Neuromuscular—*hallucinations.* Hematologic—*thrombocytopenia, eosinophilia, purpura, petechiae.* Gastrointestinal—*parotid swelling.* Endocrine—*change in blood glucose levels.* Other—*pancreatitis, hepatitis, jaundice, urinary frequency, testicular swelling, anorexia, alopecia.*

Additional Adverse Reactions Reported with Other Antidepressant Drugs: Anticholinergic—*sublingual adenitis, dilation of the urinary tract.* CNS and Neuromuscular—*delusions.* Gastrointestinal—*stomatitis, black tongue.* Endocrine—*gynecomastia.*

OVERDOSAGE: Signs and Symptoms

Toxic manifestations of ASENDIN® amoxapine overdosage differ significantly from those of other tricyclic antidepressants. Serious cardiovascular effects are seldom, if ever, observed. However, CNS effects—particularly grand mal convulsions—occur frequently, and treatment should be directed primarily toward prevention or control of seizures. Status epilepticus may develop and constitutes a neurologic emergency. Coma and acidosis are other serious complications of substantial ASENDIN overdosage in some cases. Renal failure may develop two to five days after toxic dosage, typically in those who have experienced multiple seizures.

Treatment

Treatment of ASENDIN overdosage should be symptomatic and supportive, but with special attention to prevention or control of seizures. Seizures may respond to standard anticonvulsive therapies, such as intravenous diazepam and/or phenytoin. The value of physostigmine appears less certain. Status epilepticus, should it develop, requires vigorous treatment such as that described by Delgado-Escueta, et al (N Engl J Med 1982; 306: 1337-1340).

Convulsions, when they occur, typically begin within 12 hours after ingestion. Prophylactic administration of anticonvulsant medication during this period may be of value. Treatment of renal failure, should it occur, is the same as that for non-drug-induced renal dysfunction. Serious cardiovascular effects are remarkably rare following ASENDIN overdosage, and the ECG typically remains within normal limits, except for sinus tachycardia. Hence, prolongation of the QRS interval beyond 100 milliseconds within the first 24 hours is not a useful guide to the severity of overdosage with this drug. Fatalities and, rarely, neurologic sequelae have resulted from prolonged status epilepticus in ASENDIN overdosage patients.

Rev. 12/85

REFERENCES: 1. Hekimian LJ, Friedhoff AJ, Deever E: A comparison of the onset of action and therapeutic efficacy of amoxapine and amitriptyline. *J Clin Psychiatry* 1978;39:633-637. 2. Data on file, Lederle Laboratories, Pearl River, NY. 3. Hekimian LJ, Weise CC, Friedhoff AJ: Onset of action of amoxapine and doxepin in outpatients with "mixed anxiety/depression." *J Clin Psychiatry* 1983;44:248-252; 4. Paprocki J, Bustamante LS, Barcala Peixoto MP, et al: A double-blind comparison of amoxapine and imipramine in depression. *A Folha Medica* 1977;74:199-210. 5. Fabre LF: The treatment of depression in outpatients: A controlled comparison of the onset of action of amoxapine and maprotiline. *J Clin Psychiatry* 1985;46:521-524.

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Calendar

(Continued from page A30)

M.D., Executive Vice-President, 1740 West 92nd St., Kansas City, MO 64114; 816-333-9700.

September 16–18, annual meeting, Canadian Psychiatric Association, London, Ontario. Contact Lea C. Metivier, Chief Administrative Officer, 225 Lisgar St., Suite 103, Ottawa, Ontario K2P 0C6, Canada; 613-234-2815.

September 16—20, annual convention, National Alliance for the Mentally Ill, Washington, D.C. Contact NAMI, 1901 North Ft. Myer Dr., Suite 500, Arlington, VA 22209; 703-524-7600.

September 17–18, semiannual meeting, American Board of Medical Specialties, Chicago. Contact Donald G. Langsley, M.D., Executive Vice-President, One American Plaza, Suite 805, Evanston, IL 60201; 312-491-9091.

September 18–20, child psychiatry examination, American Board of Psychiatry and Neurology, Minneapolis. Contact Stephen C. Scheiber, M.D., Executive Secretary, One American Plaza, Suite 808, Evanston, IL 60201; 312-846-0830.

September 22–25, International Symposium, Brain Acetylcholine: From Preclinical to Clinical Investigations, Taormina, Italy. Contact A.P. Caputi, M.D., Institute of Pharmacology, University of Messina, Piazza XX Settembre, 4, 98100 MESSINA (Italy); 090-712533.

September 22–27, VIIIth European Congress of Child and Adolescent Psychiatry, Varna, Bulgaria. Contact Prof. Dr. Chr. Christosov, Dept. of Psychiatry, Medical Academy, Sofia, 1431, Bulgaria.

September 24–October 1, II Annual Conference on the Foundations of Behavioral Neurology, Hong Kong. Contact Teresa Santana, Assistant Program Director, So. California Neuropsychiatric Institute, 6794 La Jolla Blvd., La Jolla, CA 92037; 619-454-2121, 800-423-9521.

September 26–29, annual meeting, Southern Psychiatric Association, Boca Raton, Fla. Contact Annette S. Boutwell, Executive Director, P.O. Box 10387, Raleigh, NC 27605; 919-821-2226.

September 27–30, annual meeting, Association of Mental Health Administrators, Hollywood, Fla. Contact Weir Richard Kirk, Executive Director, 840 North Lake Shore Dr., Suite 1103W, Chicago, IL 60611; 312-943-2751.

September 27–October 2, annual meeting, American Health Care Association, New York. Contact Paul R. Willging, Ph.D., Executive Director, 1200 15th St., N.W., 8th Fl., Washington, DC 20005-2899; 202-833-2050.

September 28–October 3, annual meeting, Pan American Health Organization, Washington, D.C. Contact Carlyle Guerra de Macedo, M.D., Director, 525 23rd St., N.W., Washington, DC 20037; 202-861-3200.

OCTOBER

October 6–11, annual meeting, American School Health Association, Indianapolis. Contact Dana A. Davis, Executive Director, P.O. Box 708, Kent, OH 44240; 216-678-1601.

October 7–10, annual meeting, American Academy for Cerebral Palsy and Developmental Medicine, Boston. Contact John A. Hinckley, Executive Director, P.O. Box 11083, Richmond, VA 23230; 804-355-0147.

October 7–10, annual meeting, American Academy of Clinical Psychiatrists, Toronto. Contact Robert Budetti, Executive Secretary, P.O. Box 3212, San Diego, CA 92103; 619-460-2675.

October 8–11, annual meeting, American Medical Care and Review Association, Monterey, Calif. Contact Ronald A. Hurst, Executive Vice-President, 5410 Grosvenor Ln., Suite 210, Bethesda, MD 20814; 301-493-9552.

October 9–12, Vth Scientific Conference of the International Federation of Psychoanalytic Societies, New York. Contact Ann R. Turkel, M.D., Secretary-General of the IFPS, 350 Central Park West, New York, NY 10025; 212-831-3400.

October 11–16, annual meeting, American College of Surgeons, San Francisco. Contact C. Rollins Hanlon, M.D., F.A.C.S., Executive Director, 55 East Erie St., Chicago, IL 60610; 312-664-4050.

October 15–17, annual meeting, Canadian Association for Community Living, Washington, D.C. Contact Jacques Peletier, Executive Vice-President, Kinsmen Bldg., York University Campus, 4700 Keele St., Downsview, Ontario M3J 1P3, Canada; 416-661-9600.

October 15–17, annual conference, Canadian Group Psychotherapy Association, Banff, Alberta, Canada. Contact Dr. Edgardo Perez, Dept. of Psychiatry, Ottawa Civic Hospital, 1053 Carling Ave., Ottawa, Ontario K1Y 4E9, Canada.

October 15–17, annual meeting, National Association for Retarded Citizens, Washington, D.C. Contact Alan Abeson, Ed.D., Executive Director, 2501 Avenue "J," Arlington, TX 76006; 817-640-0204.

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CONSULTATION/LIAISON FELLOWSHIP

The Miriam Hospital and Brown University Department of Psychiatry and Human Behavior are offering a full-time one to two year consultation/liaison fellowship beginning in July,1987. The position is open to qualified applicants who have completed an approved psychiatric residency program. In addition to clinical, teaching and administrative experience on an active inpatient consultation/liaison service, this program offers unique experience and training in a nationally recognized Division of Behavioral Medicine, with programs in Chronic Pain, Headache, Behavorial Cardiology, Psychosocial Oncology, Health Promotion and Risk Factors Management. There is ample opportunity for developing research and teaching skills and engaging in clinical research. The Miriam Hospital is a 240 bed teaching affiliate of Brown University Program in Medicine with residency programs in Internal Medicine, Psychiatry and Surgery and Health Psychology training programs. For more information, contact James R. McCartney, M.D. or Michael G. Goldstein, M.D., Department of Psychiatry, The Miriam Hospital, 164 Summit Avenue, Providence, Rhode Island 02906, 274-3700, ext. 4300. The Miriam Hospital is an Equal Opportunity Employer.

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Location: Albany, NY

NYS Office of Mental Health's Capital District Psychiatric Center (CDPC) and Albany Medical College (AMC) are seeking qualified psychiatrists to function as Unit Clinical Directors in CPDC, which is a modern and progressive JCAH accredited hospital. Clinical Directors provide clinical leadership and supervision for a 250-bed unit's interdisciplinary treatment team. Inpatient units are integrated into a full range of comprehensive mental health services (hospital and community based).

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5-mg, 10-mg, 25-mg capsules
Before prescribing, please consult complete product information, a summary of which follows:
Indications: Management of anxiety disorders; short-term relief of anxiety symptoms, acute alcohol withdrawal symptoms, preoperative apprehension and anxiety. Usually not required for anxiety or tension associated with stress of everyday life. Efficacy beyond four months not established by systematic clinical studies. Periodic reassessment of therapy recommended.
Contraindications: Known hypersensitivity to the drug.
Warnings: Warn patients that mental and/or physical abilities required for tasks such as driving or operating machinery may be impaired, as may be mental alertness in children, and that concomitant use with alcohol or CNS depressants may have an additive effect. Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms (including convulsions) reported after abrupt cessation of extended use of excessive doses are similar to those seen with barbiturates. Milder symptoms reported infrequently when continuous therapy is abruptly ended. Avoid abrupt discontinuation; gradually taper dosage.
***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically. Due to isolated reports of exacerbation, use with caution in patients with porphyria.
Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.
Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral—Adults:* Mild and moderate anxiety disorders and symptoms, 5 or 10 mg *t.i.d.* or *q.i.d.*; severe states, 20 or 25 mg *t.i.d.* or *q.i.d. Geriatric patients:* 5 mg *b.i.d.* to *q.i.d.* (See Precautions.)
Supplied: Librium® (chlordiazepoxide HCl/Roche) *Capsules*, 5 mg, 10 mg and 25 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10. Libritabs® (chlordiazepoxide/Roche) *Tablets*, 5 mg and 10 mg—bottles of 100 and 500; 25 mg—bottles of 100. With respect to clinical activity, capsules and tablets are indistinguishable.

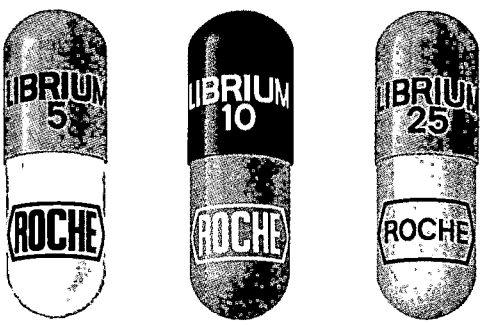
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Books Received

Psychotherapy and Culture, revised ed., by Theodora M. Abel, Rhoda Metraux, and Samuel Roll. Albuquerque, University of New Mexico, 1987, 226 pp., $29.95; $15.95 (paper).

Depression: Assessment and Treatment Update—Proceedings, by American Occupational Therapy Association. Rockville, Md., AOTA, 67 pp., $10.50 (paper).

Clinical Empathy, by David M. Berger, M.D. Northvale, N.J., Jason Aronson, 287 pp., $27.50.

The Psychology of Sport: The Behavior, Motivation, Personality and Performance of Athletes, by Dorcas Susan Butt. New York, Van Nostrand Reinhold Co., 1987, 329 pp., $21.95 (paper).

Health Professionals and Human Rights in the Philippines, by Richard P. Claude, Eric Stover, and June P. Lopez. Washington, D.C., Committee on Scientific Freedom and Responsibility, American Association for the Advancement of Science, February 1987, 86 pp., no price listed (paper).

In the Field of Fire, edited by Jeanne Van Buren Dann and Jack Dann. New York, Tor Books, 1987, 415 pp., $8.95 (paper).

The Human Brain Coloring Book, by Marian C. Diamond, Arnold B. Scheibel, and Lawrence M. Elson. New York, Barnes & Noble Books (Harper & Row), 1985, 281 pp., $9.95 (paper).

Psychosocial Assessment in Terminal Care, edited by David M. Dush, Barrie R. Cassileth, and Dennis C. Turk. New York, Haworth Press, 1986, 150 pp., $22.95.

Betty: A Glad Awakening, by Betty Ford with Chris Chase. Garden City, N.Y., Doubleday & Co., 1987, 217 pp., $16.95.

Depression in the Family, edited by Arthur Freeman, Norman Epstein, and Karen M. Simon. New York, Haworth Press, 1986, 188 pp., $29.95.

Three Papers on the Theory of Mental Health Sciences, by Joseph Garcia. Stuttgart, F.R.G., Hippokrates Verlag, 1987, 159 pp., no price listed.

Treatment of Schizophrenia: Family Assessment and Intervention, edited by Michael J. Goldstein, Iver Hand, and Kurt Hahlweg. New York, Springer-Verlag, 1986, 215 pp., $34.50 (paper).

Free to Be Human (1979), by Eugene Kennedy. Garden City, N.Y., Image Books (Doubleday & Co.), 1987, 143 pp., $6.95 (paper).

A Time for Being Human (1977), by Eugene Kennedy. Garden City, N.Y., Image Books (Doubleday & Co.), 1987, 236 pp., $7.95 (paper).

A Time for Love (1970), by Eugene C. Kennedy. Garden City, N.Y., Image Books (Doubleday & Co.), 1987, 159 pp., $4.95 (paper).

Privileged Communications in the Mental Health Professions, by Samuel Knapp and Leon VandeCreek. New York, Van Nostrand Reinhold Co., 1987, 196 pp., $29.95.

The Rape Victim: Clinical and Community Approaches to Treatment, by Mary P. Koss, Ph.D., and Mary R. Harvey, Ph.D.; edited by James Butcher. Lexington, Mass., Stephen Greene Press (New York, Penguin Books, distributor), 1987, 164 pp., $19.95.

Parenting Across the Life Span: Biosocial Dimensions, edited by Jane B. Lancaster, Jeanne Altmann, Alice S. Rossi, and Lonie R. Sherrod. New York, Aldine de Gruyter, 1987, 456 pp., $45.95.

Schizoaffective Psychoses, edited by A. Marneros and M.T. Tsuang. New York, Springer-Verlag, 1986, 318 pp., $88.00.

The Frontal Lobes Revisited, edited by Ellen Perecman. New York, IRBN Press, 1987, 306 pp., no price listed.

Psychopathological Disorders of Childhood, 3rd ed., edited by Herbert C. Quay and John S. Werry. New York, John Wiley & Sons, 1986, 660 pp., no price listed.

To Do No Harm: A Journey Through Medical School, by Philip Reilly, M.D., J.D. Dover, Mass., Auburn House Publishing Co., 1987, 292 pp., $24.95; $16.95 (paper).

Keeping Hope Alive: On Becoming a Psychotherapist (1986), by F. Robert Rodman, M.D. New York, Harper & Row, 1987, 207 pp., $7.95 (paper).

Psychotherapy: The Art of Wooing Nature, by Sheldon Roth, M.D. Northvale, N.J., Jason Aronson, 1987, 288 pp., $27.50.

Biological and Psychological Factors in Cardiovascular Disease, edited by T.H. Schmidt, T.M. Dembroski, and G. Blümchen. New York, Springer-Verlag, 1986, 623 pp, $52.00.

Sexuality and Medicine, vol. I: Conceptual Roots, edited by Earl E. Shelp. Dordrecht, The Netherlands, D. Reidel Publishing Co., 1987, 267 pp., $49.00.

Psychoanalytic Practice, I: Principles, by Helmut Thomä and Horst Kächele; translated by M. Wilson and D. Roseveare. New York, Springer-Verlag, 1987, 403 pp., $49.50.

Human Birth: An Evolutionary Perspective, by Wenda R. Trevathan. New York, Aldine de Gruyter, 1987, 259 pp., $29.95.

What Is Epilepsy? The Clinical and Scientific Basis of Epilepsy, by M.R. Trimble, F.R.C.P., F.R.C.Psych., and E.H. Reynolds, M.D., F.R.C.P., F.R.C.Psych. Edinburgh, Churchill Livingstone (White Plains, N.Y., Longman, distributor), 1986, 344 pp., $74.00.

Mental Health and Primary Care: Dutch and Israeli Experience, edited by G.J. Visser, J.M. Bensing, B.P.R. Gersons, B. Maoz, and C.Z. Margolis. Utrecht, Netherlands Institute of Primary Health Care, 1986, 217 pp., no price listed (paper).

Decision Making in Adult Neurology, by Leon A. Weisberg, M.D., Richard L. Strub, M.D., and Carlos A. Garcia, M.D. Philadelphia, B.C. Decker (St. Louis, Mosby/Times Mirror, distributor), 1987, 246 pp., no price listed.

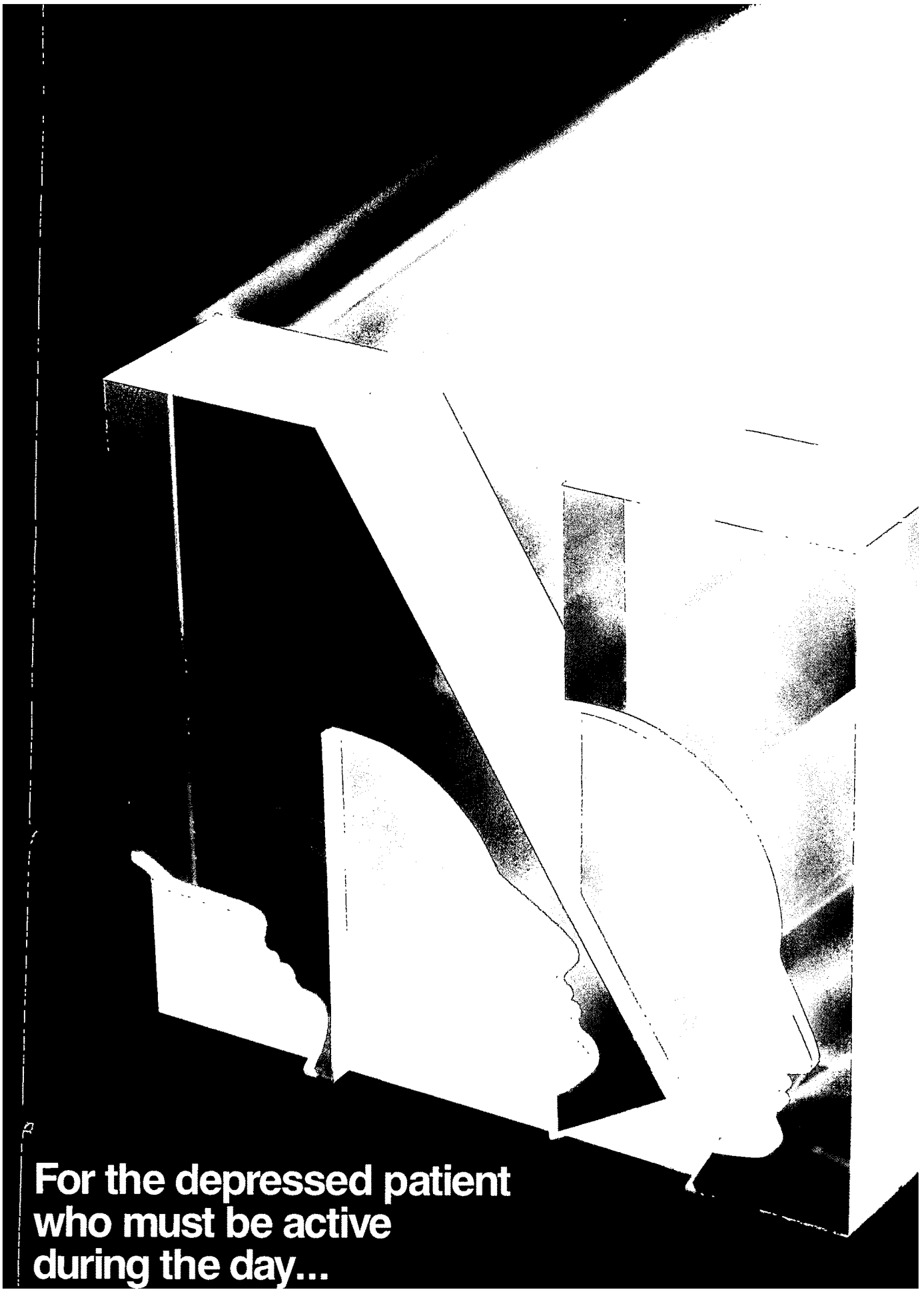
Blindsight: A Case Study and Implications, by L. Weiskrantz. Oxford, Clarendon Press (New York, Oxford University Press, distributor), 1986, 181 pp., $32.50.

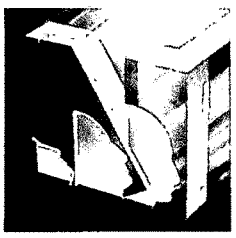
WHO Expert Committee on Drug Dependence, Twenty-third Report: World Health Organization Technical Report Series 741. Geneva, WHO, 1987, 64 pp., 9 Swiss francs (paper).

Holding and Interpretation: Fragment of an Analysis (1986), by D.W. Winnicott. New York, Grove Press (Random House, distributor), 1987, 194 pp., $18.95.

Drug Dependence and Alcohol-Related Problems: A Manual for Community Health Workers With Guidelines for Trainers, by the World Health Organization. Geneva, WHO, 1986, 34 pp., 9 Swiss francs (paper).




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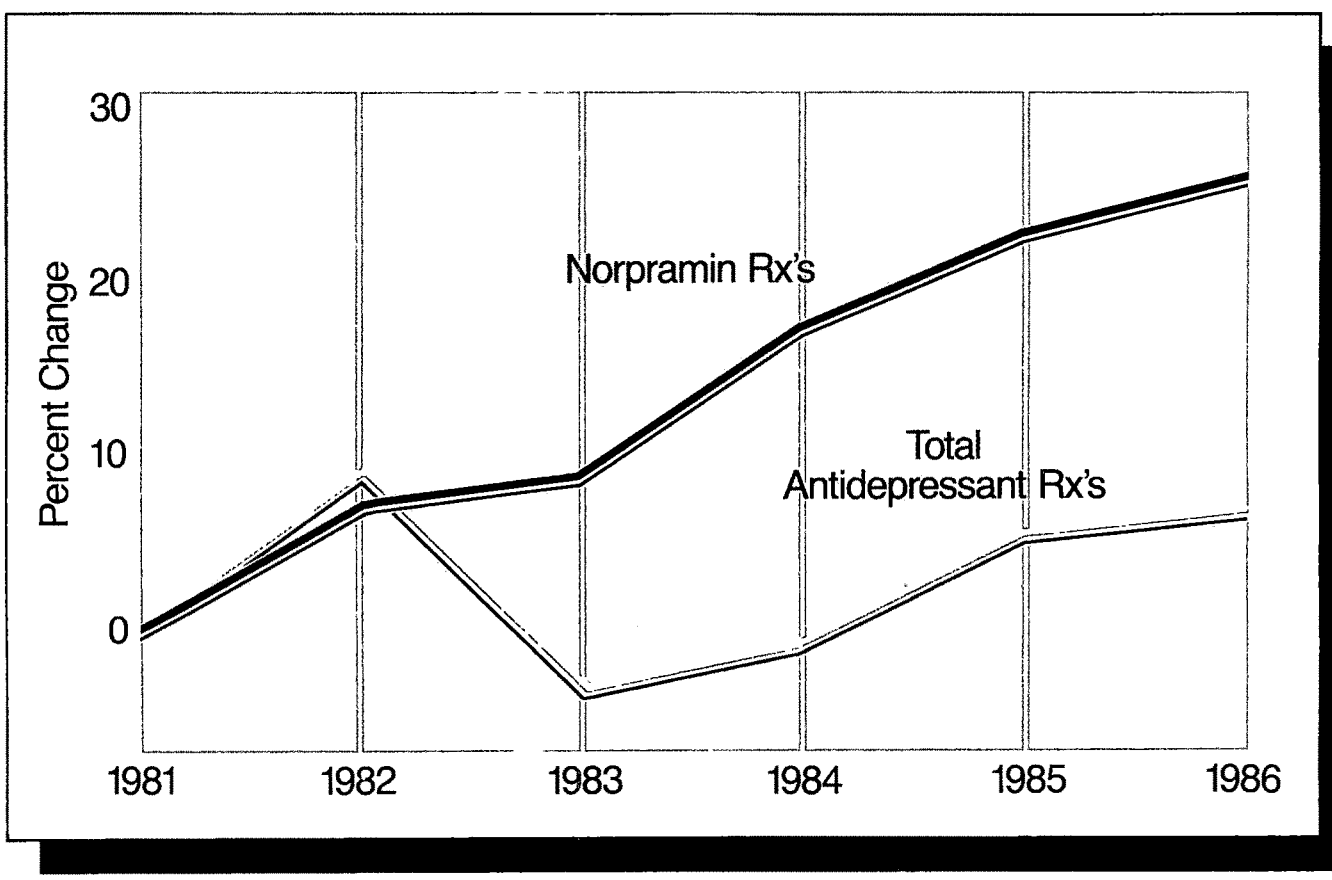


Figure 1.

The red line tracks the percent change in Norpramin prescriptions; the yellow line represents the percent change in total prescription activity for the antidepressant market (results of nationwide independent survey).

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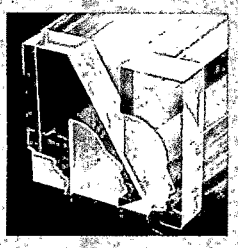
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1. Greenberg RN: Overview of patient compliance with medication dosing: A literature review. Clin Ther 6:592-599, 1984.

Brief Summary of Prescribing Information appears on the next page.



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Convenient choice of six tablet strengths and once daily or divided dosage schedule allows titration to individual response.

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The antidepressant most widely prescribed by psychiatrists

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Brief Summary

MECHANISM OF ACTION: Available evidence suggests that many depressions have a biochemical basis in the form of a relative deficiency of neurotransmitters such as norepinephrine and serotonin. Norepinephrine deficiency may be associated with relatively low urinary 3-methoxy-4-hydroxyphenyl glycol (MHPG) levels, while serotonin deficiencies may be associated with low spinal fluid levels of 5-hydroxyindolacetic acid.

While the precise mechanism of action of the tricyclic antidepressants is unknown, a leading theory suggests that they restore normal levels of neurotransmitters by blocking the reuptake of these substances from the synapse in the central nervous system.

Evidence indicates that the secondary amine tricyclic antidepressants, including Norpramin, may have greater activity in blocking the re-uptake of norepinephrine. Tertiary amine tricyclic antidepressants, such as amitriptyline, may have greater effect on serotonin re-uptake.

Norpramin (desipramine hydrochloride) is not a monoamine oxidase (MAO) inhibitor and does not act primarily as a central nervous system stimulant. It has been found in some studies to have a more rapid onset of action than imipramine. Earliest therapeutic effects may occasionally be seen in 2 to 5 days, but full treatment benefit usually requires 2 to 3 weeks to obtain.

INDICATIONS: Norpramin (desipramine hydrochloride) is indicated for relief of symptoms in various depressive syndromes, especially endogenous depression.

CONTRAINDICATIONS: Desipramine hydrochloride should not be given in conjunction with, or within 2 weeks of, treatment with an MAO inhibitor drug; hyperpyretic crises, severe convulsions, and death have occurred in patients taking MAO inhibitors and tricyclic antidepressants. When Norpramin (desipramine hydrochloride) is substituted for an MAO inhibitor, at least 2 weeks should elapse between treatments. Norpramin should then be started cautiously and should be increased gradually.

The drug is contraindicated in the acute recovery period following myocardial infarction. It should not be used in those who have shown prior hypersensitivity to the drug. Cross sensitivity between this and other dibenzazepines is a possibility.

WARNINGS: 1. Extreme caution should be used when this drug is given in the following situations: a. In patients with cardiovascular disease, because of the possibility of conduction defects, arrhythmias, tachycardias, strokes, and acute myocardial infarction. b. In patients with a history of urinary retention or glaucoma, because of the anticholinergic properties of the drug. c. In patients with thyroid disease or those taking thyroid medication, because of the possibility of cardiovascular toxicity, including arrhythmias. d. In patients with a history of seizure disorder, because this drug has been shown to lower the seizure threshold. **2.** This drug is capable of blocking the antihypertensive effect of guanethidine and similarly acting compounds. **3.** USE IN PREGNANCY: Safe use of desipramine hydrochloride during pregnancy and lactation has not been established; therefore, if it is to be given to pregnant patients, nursing mothers, or women of childbearing potential, the possible benefits must be weighed against the possible hazards to mother and child. Animal reproductive studies have been inconclusive. **4.** USE IN CHILDREN: Norpramin (desipramine hydrochloride) is not recommended for use in children since safety and effectiveness in the pediatric age group have not been established. **5.** The patient should be cautioned that this drug may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery. **6.** In patients who may use alcohol excessively, it should be borne in mind that the potentiation may increase the danger inherent in any suicide attempt or overdosage.

PRECAUTIONS: 1. It is important that this drug be dispensed in the least possible quantities to depressed outpatients, since suicide has been accomplished with this class of drug. Ordinary prudence requires that children not have access to this drug or to potent drugs of any kind; if possible, this drug should be dispensed in containers with child-resistant safety closures. Storage of this drug in the home must be supervised responsibly. **2.** If serious adverse effects occur, dosage should be reduced or treatment should be altered. **3.** Norpramin (desipramine hydrochloride) therapy in patients with manic-depressive illness may induce a hypomanic state after the depressive phase terminates. **4.** The drug may cause exacerbation of psychosis in schizophrenic patients. **5.** Close supervision and careful adjustment of dosage are required when this drug is given concomitantly with anticholinergic or sympathomimetic drugs. **6.** Patients should be warned that while taking this drug their response to alcoholic beverages may be exaggerated. **7.** Clinical experience in the concurrent administration of ECT and antidepressant drugs is limited. Thus, if such treatment is essential, the possibility of increased risk relative to benefits should be considered. **8.** If Norpramin (desipramine hydrochloride) is to be combined with other psychotropic agents such as tranquilizers or sedative/hypnotics, careful consideration should be given to the pharmacology of the agents employed since the sedative effects of Norpramin and benzodiazepines (e.g., chlordiazepoxide or diazepam) are additive. Both the sedative and anticholinergic effects of the major tranquilizers are also additive to those of Norpramin. **9.** This drug should be discontinued as soon as possible prior to elective surgery because of the possible cardiovascular effects. Hypertensive episodes have been observed during surgery in patients taking desipramine hydrochloride. **10.** Both elevation and lowering of blood sugar levels have been reported. **11.** Leukocyte and differential counts should be performed in any patient who develops fever and sore throat during therapy; the drug should be discontinued if there is evidence of pathologic neutrophil depression. **12.** Norpramin 25, 50, 75, and 100 mg tablets contain FD&C Yellow No. 5 (tartrazine), which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

ADVERSE REACTIONS: Note: Included in the following listing are a few adverse reactions that have not been reported with this specific drug. However, the pharmacologic similarities among the tricyclic antidepressant drugs require that each of the reactions be considered when Norpramin (desipramine hydrochloride) is given.

Cardiovascular: hypotension, hypertension, tachycardia, palpitation, arrhythmias, heart block, myocardial infarction, stroke.

Psychiatric: confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia and nightmares; hypomania; exacerbation of psychosis.

Neurologic: numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures; alteration in EEG patterns; tinnitus.

Anticholinergic: dry mouth, and rarely associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis, increased intraocular pressure; constipation, paralytic ileus; urinary retention; delayed micturition, dilatation of urinary tract.

Allergic: skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight), edema (of face and tongue or general), drug fever, cross sensitivity with other tricyclic drugs.

Hematologic: bone marrow depressions including agranulocytosis, eosinophilia, purpura, thrombocytopenia.

Gastrointestinal: anorexia, nausea and vomiting, epigastric distress, peculiar taste, abdominal cramps, diarrhea, stomatitis, black tongue.

Endocrine: gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence, testicular swelling; elevation or depression of blood sugar levels.

Other: jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration, flushing; urinary frequency, nocturia; parotid swelling; drowsiness, dizziness, weakness and fatigue, headache; alopecia.

Withdrawal Symptoms: Though not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

DOSAGE AND ADMINISTRATION: Not recommended for use in children. Lower dosages are recommended for elderly patients and adolescents. Lower dosages are also recommended for outpatients compared to hospitalized patients, who are closely supervised. Dosage should be initiated at a low level and increased according to clinical response and any evidence of intolerance. Following remission, maintenance medication may be required for a period of time and should be at the lowest dose that will maintain remission.

Usual Adult Dose: The usual adult dose is 100 to 200 mg per day. In more severely ill patients, dosage may be further increased gradually to 300 mg/day if necessary. Dosages above 300 mg/day are not recommended.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response.

Treatment of patients requiring as much as 300 mg should generally be initiated in hospitals, where regular visits by the physician, skilled nursing care, and frequent electrocardiograms (ECG's) are available.

The best available evidence of impending toxicity from very high doses of Norpramin is prolongation of the QRS or QT intervals on the ECG. Prolongation of the PR interval is also significant, but less closely correlated with plasma levels. Clinical symptoms of intolerance, especially drowsiness, dizziness, and postural hypotension, should also alert the physician to the need for reduction in dosage. Plasma desipramine measurement would constitute the optimal guide to dosage monitoring.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

Adolescent and Geriatric Dose: The usual adolescent and geriatric dose is 25 to 100 mg daily.

Dosage should be initiated at a lower level and increased according to tolerance and clinical response to a usual maximum of 100 mg daily. In more severely ill patients, dosage may be further increased to 150 mg/day. Doses above 150 mg/day are not recommended in these age groups.

Initial therapy may be administered in divided doses or a single daily dose.

Maintenance therapy may be given on a once-daily schedule for patient convenience and compliance.

OVERDOSAGE: See prescribing information for a discussion of symptoms and treatment of overdose.

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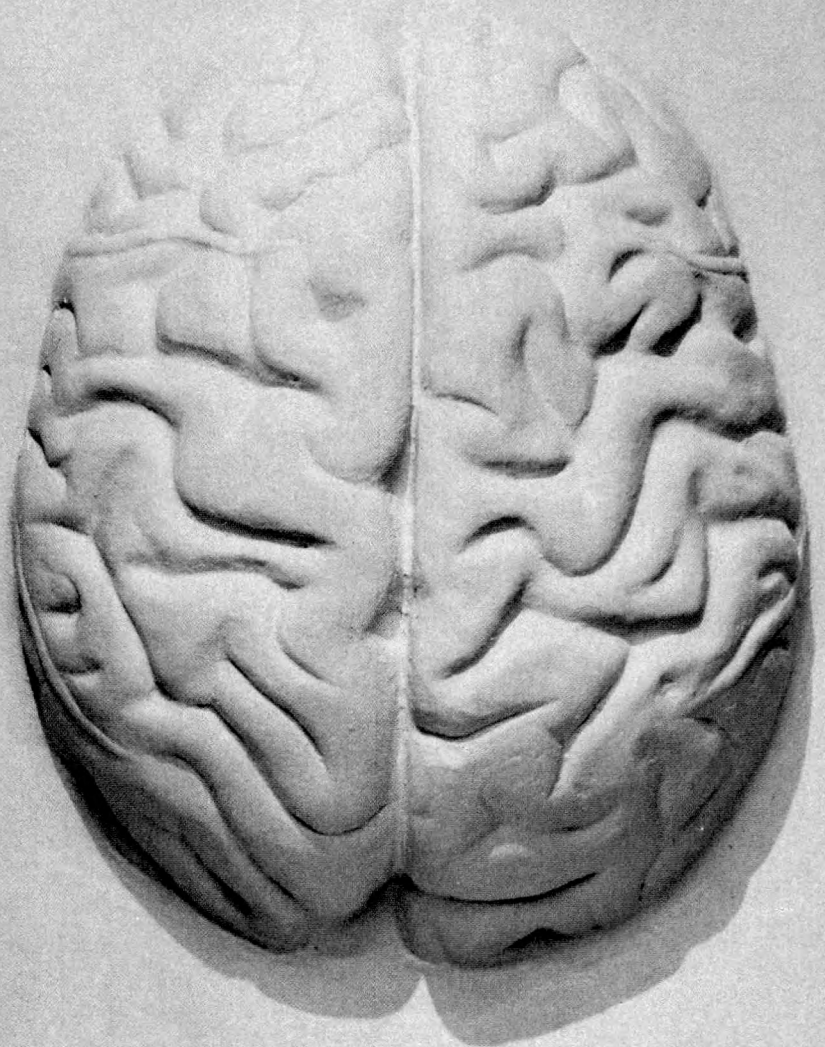
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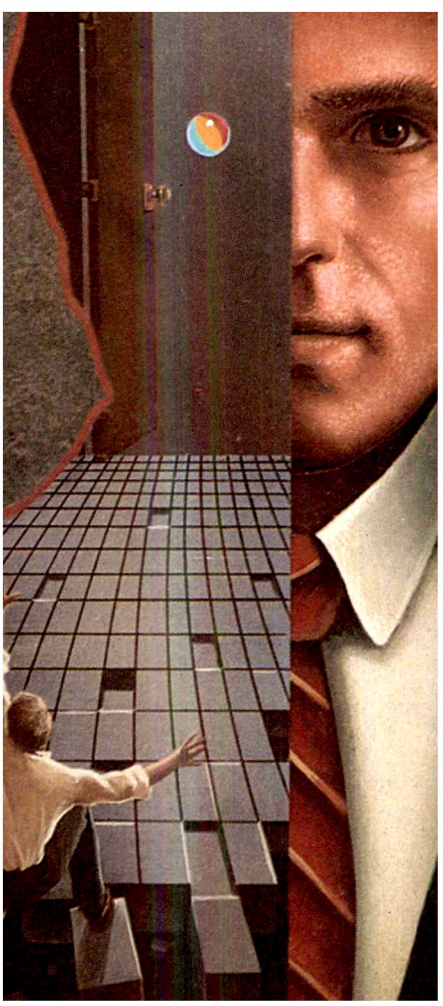
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Generally avoid using in patients hypersensitive (e.g., have had blood dyscrasias, jaundice) to any phenothiazine. Caution patients about activities requiring alertness (e.g., operating vehicles or machinery), especially during the first few days' therapy. Additive depressant effect is possible with other C.N.S. depressants, including alcohol. Do not use in pregnancy except when essential and potential benefits clearly outweigh possible hazards. Prolonged jaundice, extrapyramidal signs, hyperreflexia and hyporeflexia have been reported in newborns whose mothers received phenothiazines. There is evidence that phenothiazines are excreted in the breast milk of nursing mothers.

Precautions: Since some patients chronically exposed to neuroleptics will develop tardive dyskinesia, it is advised that, if possible, full information about this risk be given to patients or their guardians when chronic use is contemplated.

Use cautiously in angina. Avoid high doses and parenteral use when cardiovascular system is impaired since hypotension has occurred. Antiemetic effect may mask the signs of overdosage of other drugs or obscure diagnosis and treatment of certain physical disorders. Prolonged use of high doses may result in cumulative effects with severe C.N.S. or vasomotor symptoms. If retinal changes occur, discontinue drug. Agranulocytosis, thrombocytopenia, pancytopenia, anemia, cholestatic jaundice, liver damage have been reported. Use cautiously in patients with glaucoma.

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Phenothiazines may diminish the effect of oral anticoagulants. Phenothiazines can produce alpha-adrenergic blockade. Concomitant use of phenothiazines with propranolol increases plasma levels of both drugs. Concurrent use of phenothiazines may counteract antihypertensive effects of guanethidine and related compounds. Thiazide diuretics may accentuate the orthostatic hypotension that may occur with phenothiazines. Phenothiazines may lower the convulsive threshold and may also precipitate phenytoin toxicity; dosage adjustments of anticonvulsants may be necessary. If neuromuscular reactions occur in pregnant women, or in children, permanently stop neuroleptic therapy. Patients should not receive 'Stelazine' 48 hours before or 24 hours after myelography with the contrast medium metrizamide. The presence of phenothiazines may produce false positive phenylketonuria (PKU) test results.

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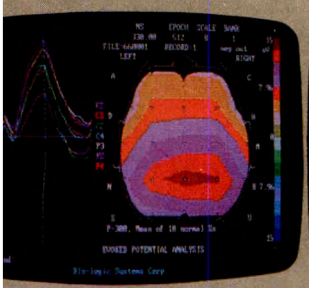
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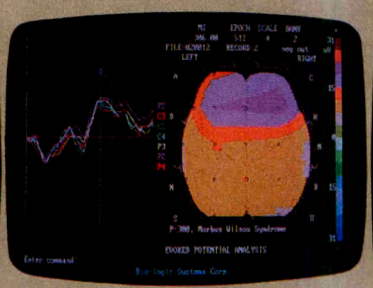
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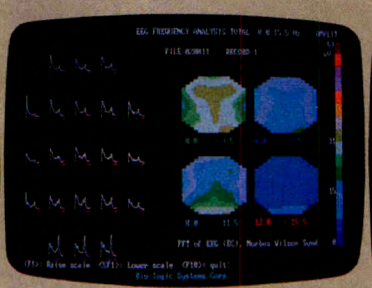
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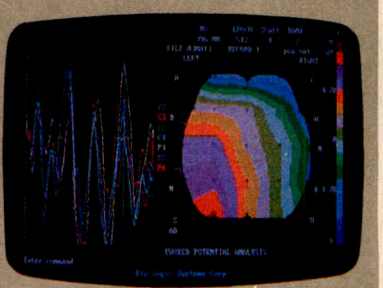
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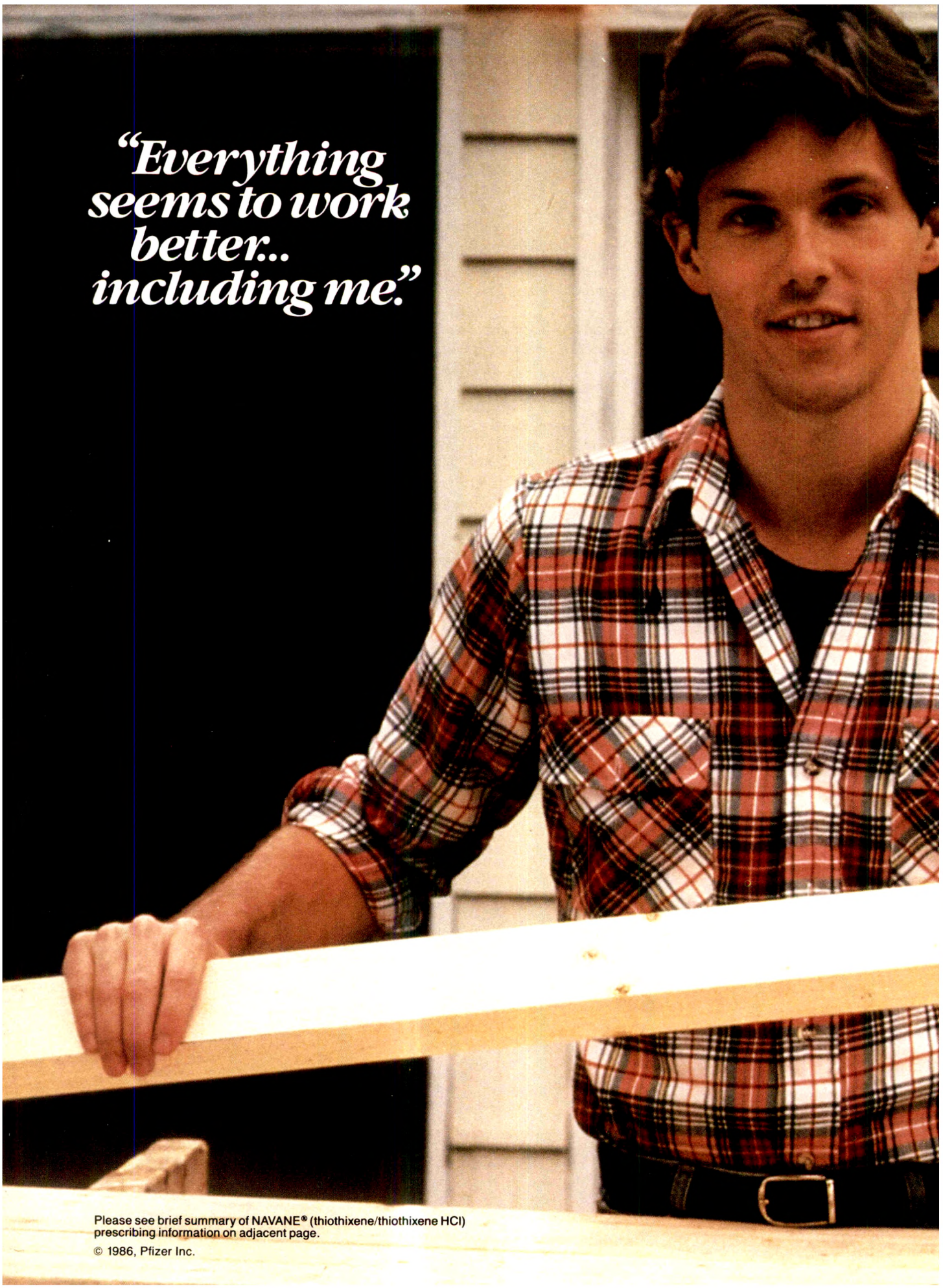
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Please see brief summary of NAVANE® (thiothixene/thiothixene HCl) prescribing information on adjacent page.

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IT FEELS GOOD TO FEEL USEFUL AGAIN

For the chronic psychotic patient, Navane can mean improved motivation[1] and more competent work performance.[2,3] Improvement generally occurs without serious side effects. Anticholinergic[4] and cardiovascular[5,6] side effects are reported infrequently. Should extrapyramidal symptoms occur, they usually can be controlled.

Navane®
(thiothixene) (thiothixene HCl)

ROERIG Pfizer
A division of Pfizer Pharmaceuticals
New York, New York 10017
at the forefront of psychopharmacology

References: **1** Bressler B, Friedel RO: A comparison between chlorpromazine and thiothixene in a Veterans Administration hospital population. *Psychosomatics* 1971;12:275-277. **2** DiMascio A, Demirgian E: Study of the activating properties of thiothixene. *Psychosomatics* 1972;13:105-108. **3** DiMascio A, Demirgian E: Job training in the rehabilitation of the chronic schizophrenic. Presented as a Scientific Exhibit at The American Psychiatric Association. Washington, DC, May 3-6, 1971. **4** Goldstein B, Weiner D, Banas F: Clinical evaluation of thiothixene in chronic ambulatory schizophrenic patients, in Lehmann HE, Ban TA (eds): *The Thioxanthenes: Modern Problems of Pharmacopsychiatry.* Basel, Switzerland, S Karger, 1969, vol 2, pp 45-52. **5** Dillenkoffer RL, Gallant DM, George RB, et al: Electrocardiographic evaluation of schizophrenic patients: A double-blind comparison. Presented as a Scientific Exhibit at The 125th Annual Meeting of The American Psychiatric Association, Dallas, May 1-4, 1972. **6** Data available on request from Roerig.

BRIEF SUMMARY OF PRESCRIBING INFORMATION
Navane® (thiothixene) Capsules: 1 mg, 2 mg, 5 mg, 10 mg, 20 mg
(thiothixene hydrochloride) Concentrate: 5 mg/ml, Intramuscular: 2 mg/ml, 5 mg/ml

Contraindications: Navane (thiothixene) is contraindicated in patients with circulatory collapse, comatose states, central nervous system depression due to any cause, and blood dyscrasias. Navane is contraindicated in individuals who have shown hypersensitivity to the drug. It is not known whether there is a cross-sensitivity between the thioxanthenes and the phenothiazine derivatives, but the possibility should be considered.

Warnings: *Tardive Dyskinesia*—Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with neuroleptic (antipsychotic) drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of neuroleptic treatment, which patients are likely to develop the syndrome. Whether neuroleptic drug products differ in their potential to cause tardive dyskinesia is unknown.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of neuroleptic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if neuroleptic treatment is withdrawn. Neuroleptic treament, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying disease process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, neuroleptics should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic neuroleptic treatment should generally be reserved for patients who suffer from a chronic illness that, 1) is known to respond to neuroleptic drugs, and, 2) for whom alternative, equally effective, but potentially less harmful treatments are *not* available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on neuroleptics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome.

(For further information about the description of tardive dyskinesia and its clinical detection, please refer to the section on Adverse Reactions.)

Usage in Pregnancy—Safe use of Navane during pregnancy has not been established. Therefore, this drug should be given to pregnant patients only when, in the judgment of the physician, the expected benefits from the treatment exceed the possible risks to mother and fetus. Animal reproduction studies and clinical experience to date have not demonstrated any teratogenic effects.

In the animal reproduction studies with Navane, there was some decrease in conception rate and litter size, and an increase in resorption rate in rats and rabbits, changes which have been similarly reported with other psychotropic agents. After repeated oral administration of Navane to rats (5 to 15 mg/kg/day), rabbits (3 to 50 mg/kg/day), and monkeys (1 to 3 mg/kg/day) before and during gestation, no teratogenic effects were seen. (See Precautions.)

Usage in Children—The use of Navane in children under 12 years of age is not recommended because safety and efficacy in the pediatric age group have not been established.

As is true with many CNS drugs, Navane may impair the mental and/or physical abilities required for the performance of potentially hazardous tasks such as driving a car or operating machinery, especially during the first few days of therapy. Therefore, the patient should be cautioned accordingly.

As in the case of other CNS-acting drugs, patients receiving Navane should be cautioned about the possible additive effects (which may include hypotension) with CNS depressants and with alcohol.

Precautions: An antiemetic effect was observed in animal studies with Navane; since this effect may also occur in man, it is possible that Navane may mask signs of overdosage of toxic drugs and may obscure conditions such as intestinal obstruction and brain tumor.

In consideration of the known capability of Navane and certain other psychotropic drugs to precipitate convulsions, extreme caution should be used in patients with a history of convulsive disorders or those in a state of alcohol withdrawal since it may lower the convulsive threshold. Although Navane potentiates the actions of the barbiturates, the dosage of the anticonvulsant therapy should not be reduced when Navane is administered concurrently.

Caution as well as careful adjustment of the dosage is indicated when Navane is used in conjunction with other CNS depressants other than anticonvulsant drugs.

Though exhibiting rather weak anticholinergic properties, Navane should be used with caution in patients who are known or suspected to have glaucoma, or who might be exposed to extreme heat, or who are receiving atropine or related drugs.

Use with caution in patients with cardiovascular disease.

Also, careful observation should be made for pigmentary retinopathy, and lenticular pigmentation (fine lenticular pigmentation has been noted in a small number of patients treated with Navane for prolonged periods). Blood dyscrasias (agranulocytosis, pancytopenia, thrombocytopenic purpura), and liver damage (jaundice, biliary stasis) have been reported with related drugs.

Undue exposure to sunlight should be avoided. Photosensitive reactions have been reported in patients on Navane.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of neuroleptic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

Intramuscular Administration—As with all intramuscular preparations, Navane Intramuscular should be injected well within the body of a relatively large muscle. The preferred sites are the upper outer quadrant of the buttock (i.e. gluteus maximus) and the mid-lateral thigh.

The deltoid area should be used only if well developed, such as in certain adults and older children, and then only with caution to avoid radial nerve injury. Intramuscular injections should not be made into the lower and mid-thirds of the upper arm. As with all intramuscular injections, aspiration is necessary to help avoid inadvertent injection into a blood vessel.

Adverse Reactions: *Note:* Not all of the following adverse reactions have been reported with Navane (thiothixene). However, since Navane has certain chemical and pharmacologic similarities to the phenothiazines, all of the known side effects and toxicity associated with phenothiazine therapy should be borne in mind when Navane is used.

Cardiovascular effects: Tachycardia, hypotension, lightheadedness, and syncope. In the event hypot occurs, epinephrine should not be used as a pressor agent since a paradoxical further lowering of bloo sure may result. Nonspecific EKG changes have been observed in some patients receiving Navane (thioth These changes are usually reversible and frequently disappear on continued Navane therapy. The incid these changes is lower than that observed with some phenothiazines. The clinical significance of these cl is not known.

CNS effects: Drowsiness, usually mild, may occur although it usually subsides with continuation of t therapy. The incidence of sedation appears similar to that of the piperazine group of phenothiazines, b than that of certain aliphatic phenothiazines. Restlessness, agitation and insomnia have been note Navane. Seizures and paradoxical exacerbation of psychotic symptoms have occurred with Navane infreq

Hyperreflexia has been reported in infants delivered from mothers having received structurally related

In addition, phenothiazine derivatives have been associated with cerebral edema and cerebrospina abnormalities.

Extrapyramidal symptoms, such as pseudo-parkinsonism, akathisia, and dystonia have been reported agement of these extrapyramidal symptoms depends upon the type and severity. Rapid relief of acute syn may require the use of an injectable antiparkinson agent. More slowly emerging symptoms may be mana reducing the dosage of Navane and/or administering an oral antiparkinson agent.

Persistent Tardive Dyskinesia: As with all antipsychotic agents tardive dyskinesia may appear in so tients on long term therapy or may occur after drug therapy has been discontinued. The risk seems to be in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some p appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the t face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing mover Sometimes these may be accompanied by involuntary movements of extremities

Since early detection of tardive dyskinesia is important, patients should be monitored on an ongoing It has been reported that fine vermicular movement of the tongue may be an early sign of the syndrome or any other presentation of the syndrome is observed, the clinician should consider possible discontir of neuroleptic medication. (See Warnings section.)

Hepatic Effects: Elevations of serum transaminase and alkaline phosphatase, usually transient, have b frequently observed in some patients. No clinically confirmed cases of jaundice attributable to Navane ha reported.

Hematologic Effects: As is true with certain other psychotropic drugs, leukopenia and leukocytosis, wh usually transient, can occur occasionally with Navane. Other antipsychotic drugs have been associat agranulocytosis, eosinophilia, hemolytic anemia, thrombocytopenia and pancytopenia.

Allergic Reactions: Rash, pruritus, urticaria, photosensitivity and rare cases of anaphylaxis have b ported with Navane. Undue exposure to sunlight should be avoided. Although not experienced with Nava foliative dermatitis and contact dermatitis (in nursing personnel) have been reported with phenothiazines.

Endocrine Disorders: Lactation, moderate breast enlargement and amenorrhea have occurred in a sm centage of females receiving Navane. If persistent, this may necessitate a reduction in dosage or the dis uation of therapy. Phenothiazines have been associated with false positive pregnancy tests, gyneco hypoglycemia, hyperglycemia, and glycosuria.

Autonomic Effects: Dry mouth, blurred vision, nasal congestion, constipation, increased sweating, inc salivation, and impotence have occurred infequently with Navane therapy. Phenothiazines have been ass with miosis, mydriasis, and adynamic ileus.

Other Adverse Reactions: Hyperpyrexia, anorexia, nausea, vomiting, diarrhea, increase in appet weight, weakness or fatigue, polydipsia and peripheral edema.

Although not reported with Navane, evidence indicates there is a relationship between phenothiazine and the occurrence of a systemic lupus erythematosus-like syndrome.

NOTE: Sudden deaths have occasionally been reported in patients who have received certain phenot derivatives. In some cases the cause of death was apparently cardiac arrest or asphyxia due to failur cough reflex. In others, the cause could not be determined nor could it be established that death was phenothiazine administration.

Dosage and Administration: Dosage of Navane should be individually adjusted depending on the ch and severity of the condition. In general, small doses should be used initially and gradually increase optimal effective level, based on patient response.

Some patients have been successfully maintained on once-a-day Navane therapy.

Usage in children under 12 years of age is not recommended because safe conditions for its use have n established.

Navane Intramuscular Solution: Navane For Injection—When more rapid control and treatment of ac havior is desirable, the intramuscular form of Navane may be indicated. It is also of benefit where the very of the patient's symptomatology, whether acute or chronic, renders oral administration impractical impossible.

For treatment of acute symptomatology or in patients unable or unwilling to take oral medication, th dose is 4 mg of Navane Intramuscular administered 2 to 4 times daily. Dosage may be increased or de depending on response. Most patients are controlled on a total daily dosage of 16 to 20 mg. The maxim ommended dosage is 30 mg/day. An oral form should supplant the injectable form as soon as possible. be necessary to adjust the dosage when changing from the intramuscular to oral dosage forms. Dosage mendations for Navane (thiothixene) Capsules and Concentrate appear in the following paragraphs.

Navane Capsules: Navane Concentrate—In milder conditions, an initial dose of 2 mg three times indicated, a subsequent increase to 15 mg/day total daily dose is often effective.

In more severe conditions, an initial dose of 5 mg twice daily.

The usual optimal dose is 20 to 30 mg daily. If indicated, an increase to 60 mg/day total daily dose effective. Exceeding a total daily dose of 60 mg rarely increases the beneficial response.

Overdosage: Manifestations include muscular twitching, drowsiness, and dizziness. Symptoms o overdosage may include CNS depression, rigidity, weakness, torticollis, tremor, salivation, dys hypotension, disturbances of gait, or coma.

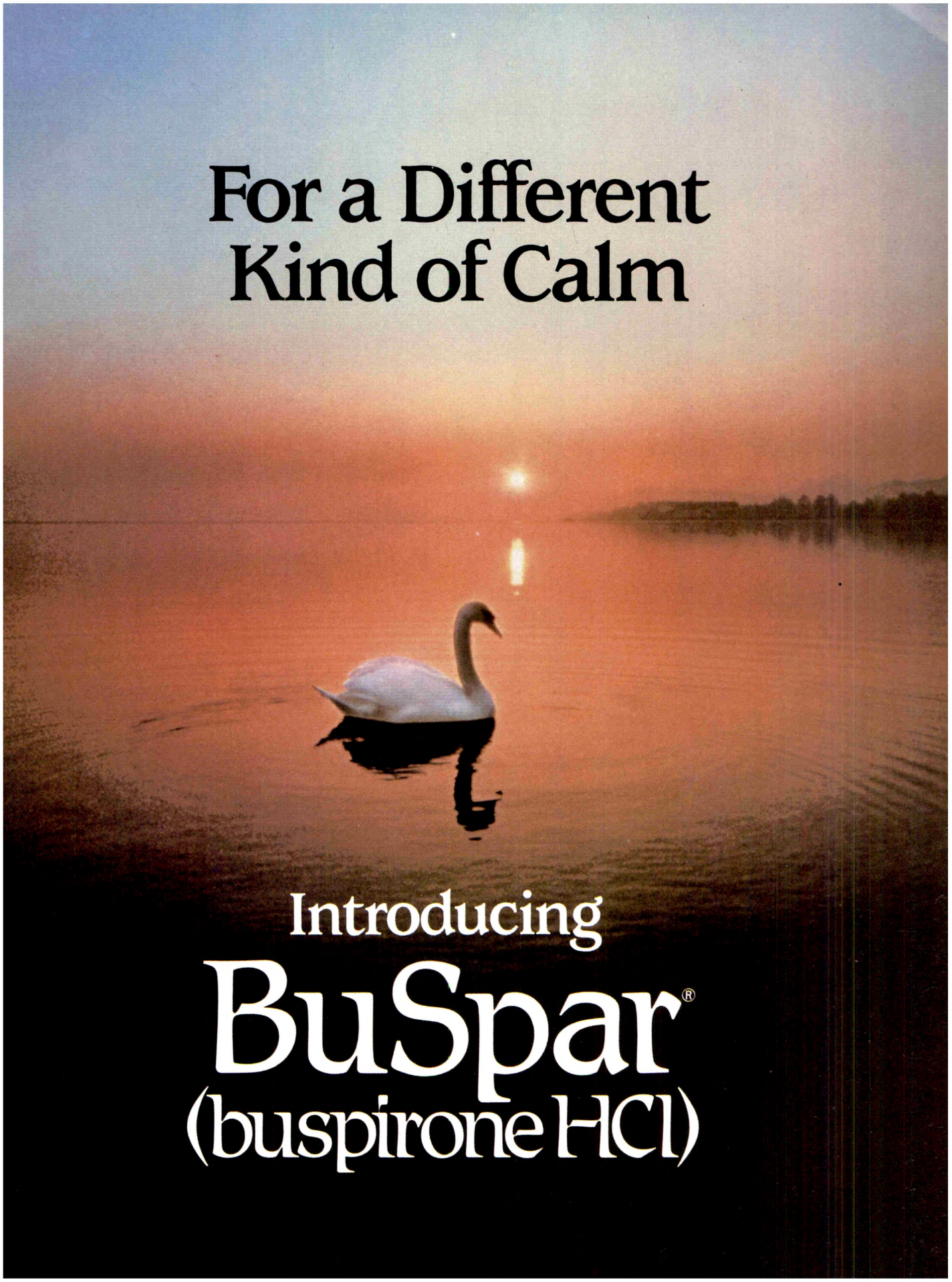
Treatment: Essentially is symptomatic and supportive. For Navane oral, early gastric lavage is help Navane oral and intramuscular, keep patient under careful observation and maintain an open airway, si volvement of the extrapyramidal system may produce dysphagia and respiratory difficulty in severe overc If hypotension occurs, the standard measures for managing circulatory shock should be used (I.V. flui or vasoconstrictors.)

If a vasoconstrictor is needed, levarterenol and phenylephrine are the most suitable drugs. Other agents, including epinephrine, are not recommended, since phenothiazine derivatives may reverse th pressor action of these agents and cause further lowering of the blood pressure.

If CNS depression is present and specific therapy is indicated, recommended stimulants include an mine, dextroamphetamine, or caffeine and sodium benzoate. Stimulants that may cause convulsions (e.g toxin or pentylenetetrazol) should be avoided. Extrapyramidal symptoms may be treated with antiparkinsor

There are no data on the use of peritoneal or hemodialysis, but they are known to be of little value nothiazine intoxication.

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A division of Pfizer Pharmaceuticals
New York, New York 10017


For a Different
Kind of Calm
Introducing
BuSpar®
(buspirone HCl)

Mead Johnson
Pharmaceuticals
Introduces

BuSpar®
Tablets
5 mg and 10 mg

(buspirone HCl)

A different kind of calm

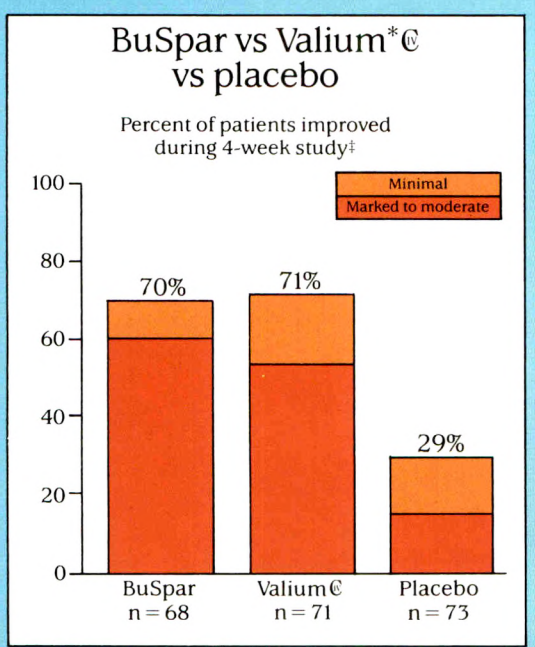
BuSpar—the first anxiolytic without CNS-depressant activity—has broken the connection between efficacy and unwanted sedative effects.

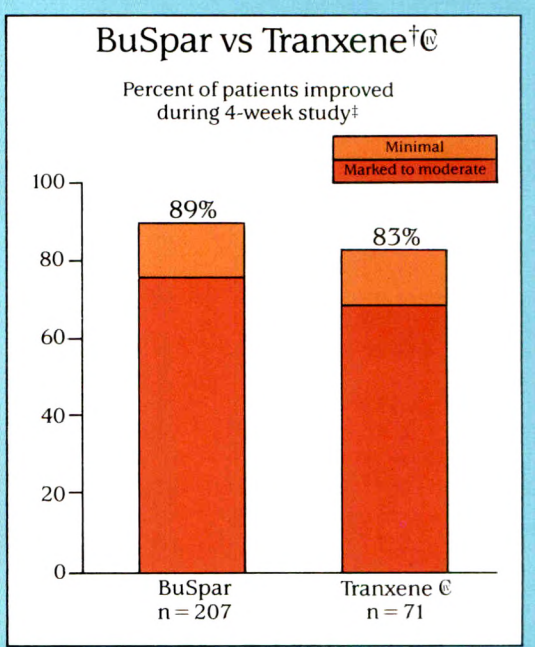
BuSpar gradually and comfortably provides relief of anxious symptoms—but produces no more drowsiness, motor impairment, or interaction with alcohol than does placebo.[1,2,3]

Furthermore, in clinical studies, BuSpar exhibited no apparent abuse liability, and no withdrawal syndrome has been reported at the end of therapy.[4,5]

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Proven anxiolytic effectiveness over a 4-week course of therapy[6,7]



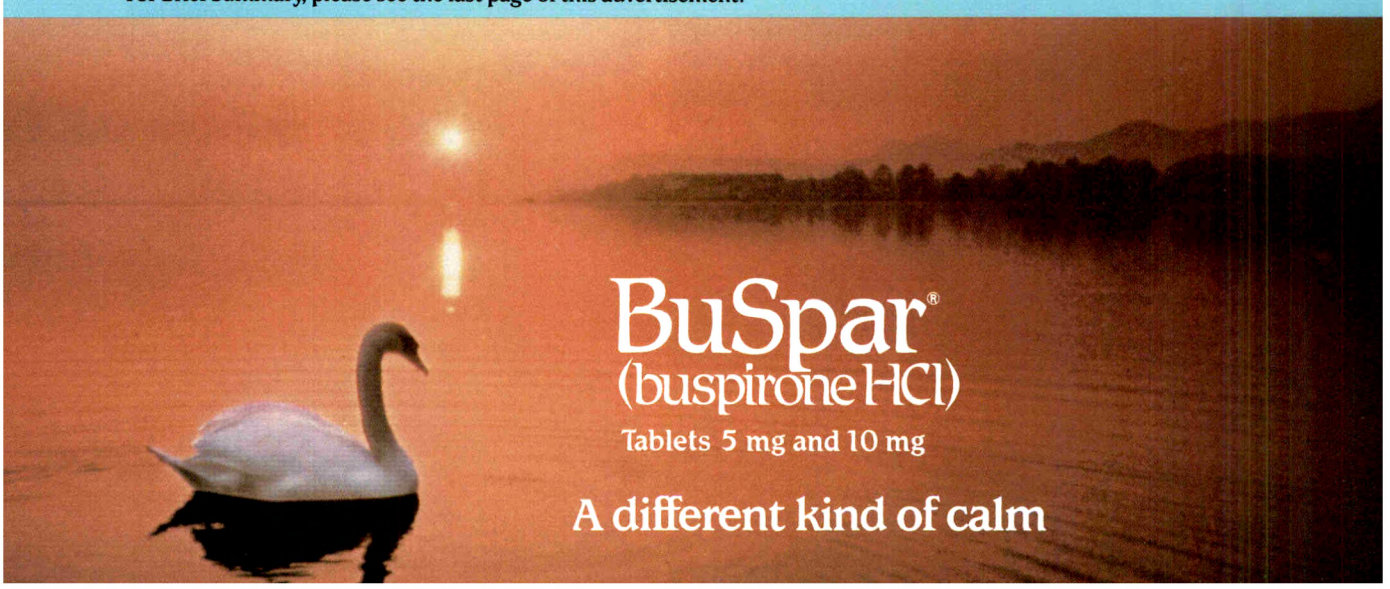


*Registered trademark of Hoffmann-La Roche Inc for diazepam.
†Registered trademark of Abbott Pharmaceuticals, Inc for clorazepate.
‡Physician's assessment of global improvement.

Extensive clinical trials have shown that BuSpar produces impressive results over a four-week course of therapy. In comparative trials with Valium and Tranxene, 70% to 89% of patients receiving BuSpar were judged by their physicians to be improved at the end of therapy. Significant improvement was noted in a wide range of anxiety-related symptoms such as anxious mood, depressed mood,* and cardiovascular and gastrointestinal complaints.

*BuSpar is not indicated for the treatment of primary depressive disorder.

For Brief Summary, please see the last page of this advertisement.



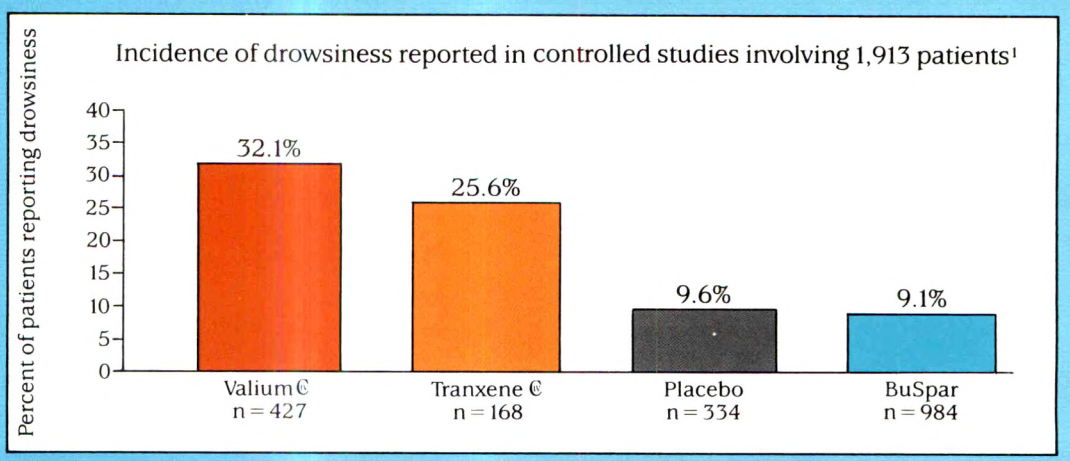
BuSpar®
Tablets
5 mg and 10 mg

(buspirone HCl)

Anxiolytic efficacy without CNS-depressant activity

Incidence of drowsiness no greater than placebo

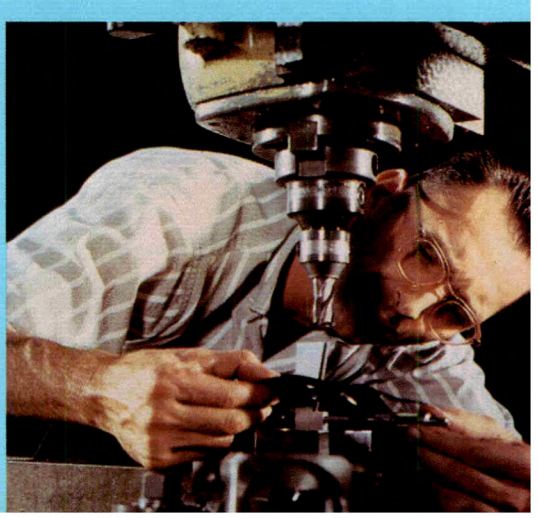
Because BuSpar does not replace symptoms with sedation, patients are alert and aware as well as anxiety-free during their waking hours.[1]



No impairment of motor skills

Controlled studies show that, unlike diazepam, BuSpar did not interfere with driving skills in normal subjects.[2]

NOTE: Patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that BuSpar treatment does not affect them adversely.





No potentiation of the effects of alcohol

A controlled study in normal subjects showed that, unlike lorazepam, BuSpar did not augment the effects of alcohol.*[3]

No apparent abuse liability

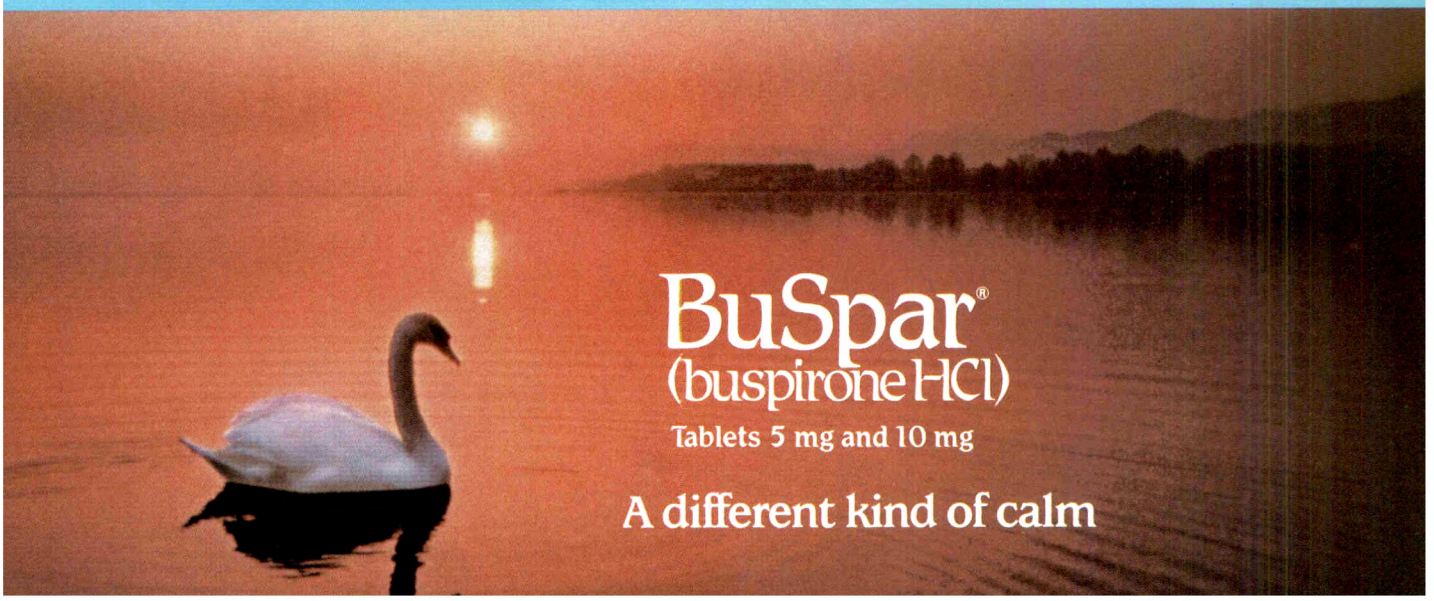
Extensive preclinical information and clinical data from studies in two populations, recreational users of sedatives and alcohol-dependent patients, demonstrate that BuSpar does not have the characteristics of common substances of abuse. Therefore, BuSpar is not a controlled substance.[4,8]

Well tolerated...with a low incidence of troublesome side effects

The most commonly observed adverse effects in controlled trials were dizziness (12%), nausea (8%), headache (6%), nervousness (5%), light-headedness (3%), and excitement (2%).

*While formal studies of the interaction of BuSpar with alcohol indicate that BuSpar does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and BuSpar.

For Brief Summary, please see the last page of this advertisement.



BuSpar®
Tablets
5 mg and 10 mg

(buspirone HCl)

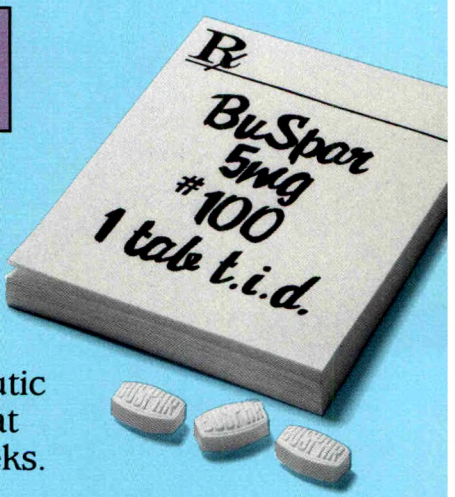
Subtle onset of effect

BuSpar relieves the symptoms of anxiety gradually and steadily. Generally, improvement will be noticeable within the first 7-10 days.

Prescribing recommendations

Initial dosage—5 mg t.i.d.

Week 1	5 mg	5 mg	5 mg



Dosage adjustment—5 mg/day increments, every 2-3 days, as needed, up to 60 mg/day.

Optimal daily dose—20-30 mg in divided doses, in most patients.

Length of therapy—To achieve full therapeutic benefit from BuSpar, it is recommended that treatment be prescribed for at least 3-4 weeks.

At the end of therapy

BuSpar therapy may be discontinued by simply stopping administration.

BuSpar is <u>not</u> a controlled substance.

Patient selection

BuSpar will not block the benzodiazepine withdrawal syndrome...therefore, the best candidates for BuSpar are those not currently taking benzodiazepines.

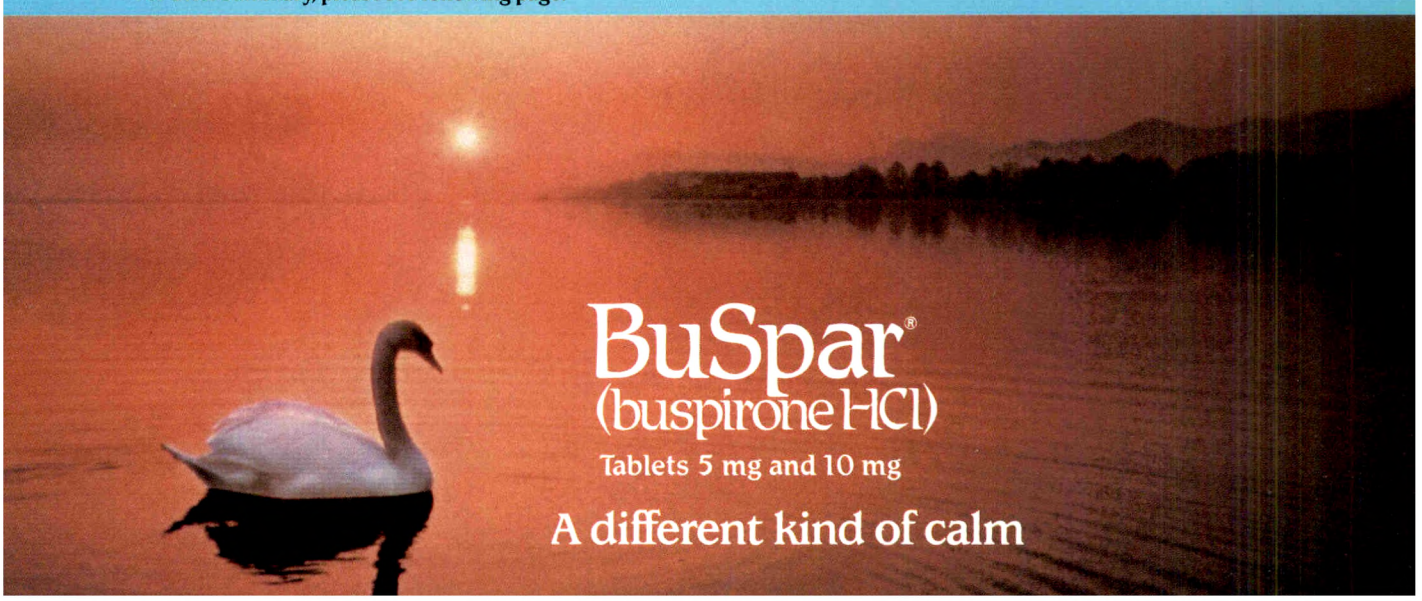
If you elect to switch a patient from a benzodiazepine to BuSpar:

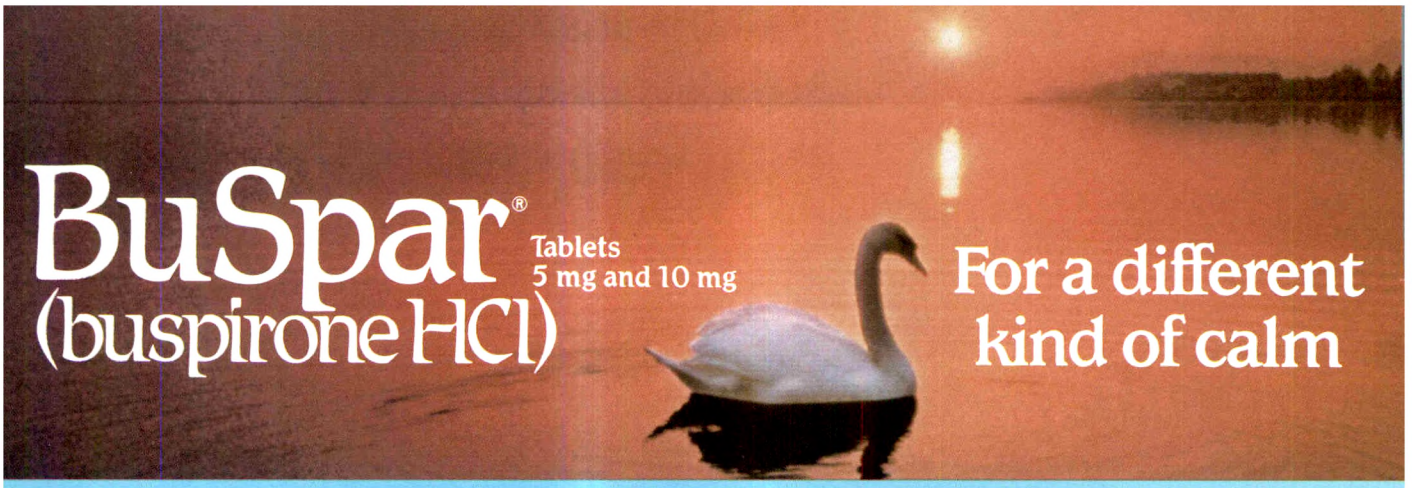
1. Carefully and completely withdraw the patient from the benzodiazepine according to the benzodiazepine manufacturer's instructions before initiating BuSpar therapy.
2. Remember that benzodiazepine withdrawal symptoms, such as irritability, anxiety, agitation, insomnia, sweating, and sometimes even seizures, may occur over varying time periods after discontinuation.

BuSpar...the first choice in anxiolytic therapy when:

- ☑ Treatment requires regular dosing for more than a few days
- ☑ Patient functioning is key to safe and successful treatment
- ☑ The potential for drug habituation, dependence, abuse, or a withdrawal syndrome is a concern

For Brief Summary, please see following page.





CONTRAINDICATIONS:
Hypersensitivity to buspirone.

WARNINGS:
The administration of BuSpar to a patient taking a monoamine oxidase inhibitor (MAOI) may pose a hazard. There have been reports of the occurrence of elevated blood pressure when BuSpar has been added to a regimen including an MAOI. Therefore, it is recommended that BuSpar not be used concomitantly with an MAOI.

Because BuSpar has no established antipsychotic activity, it should not be employed in lieu of appropriate antipsychotic treatment.

PRECAUTIONS:
General—
Interference with cognitive and motor performance:
Studies indicate that BuSpar is less sedating than other anxiolytics and that it does not produce significant functional impairment. However, its CNS effects in any individual patient may not be predictable. Therefore, patients should be cautioned about operating an automobile or using complex machinery until they are reasonably certain that buspirone treatment does not affect them adversely.

While formal studies of the interaction of BuSpar with alcohol indicate that buspirone does not increase alcohol-induced impairment in motor and mental performance, it is prudent to avoid concomitant use of alcohol and buspirone.

Potential for withdrawal reactions in sedative/hypnotic/anxiolytic drug-dependent patients:
Because BuSpar does not exhibit cross-tolerance with benzodiazepines and other common sedative/hypnotic drugs, it will not block the withdrawal syndrome often seen with cessation of therapy with these drugs. Therefore, before starting therapy with BuSpar, it is advisable to withdraw patients gradually, especially patients who have been using a CNS depressant drug chronically, from their prior treatment. Rebound or withdrawal symptoms may occur over varying time periods, depending in part on the type of drug, and its effective half-life of elimination.

The syndrome of withdrawal from sedative/hypnotic/anxiolytic drugs can appear as any combination of irritability, anxiety, agitation, insomnia, tremor, abdominal cramps, muscle cramps, vomiting, sweating, flu-like symptoms without fever, and occasionally, even as seizures.

Possible concerns related to buspirone's binding to dopamine receptors:
Because buspirone can bind to central dopamine receptors, a question has been raised about its potential to cause acute and chronic changes in dopamine mediated neurological function (e.g., dystonia, pseudoparkinsonism, akathisia, and tardive dyskinesia). Clinical experience in controlled trials has failed to identify any significant neuroleptic-like activity; however, a syndrome of restlessness, appearing shortly after initiation of treatment, has been reported in some small fraction of buspirone-treated patients. The syndrome may be explained in several ways. For example, buspirone may increase central noradrenergic activity; alternatively, the effect may be attributable to dopaminergic effects (i.e., represent akathisia). Obviously, the question cannot be totally resolved at this point in time. Generally, long-term sequelae of any drug's use can be identified only after several years of marketing.

Information for Patients:
Patients should be instructed to inform their physician about any medications, prescription or non-prescription, alcohol or drugs they are now taking or plan to take during treatment with buspirone; to inform their physician if they are pregnant, are planning to become pregnant, or become pregnant while taking buspirone; to inform their physician if they are breast feeding; and not to drive a car or operate potentially dangerous machinery until they experience how this medication affects them.

Drug Interactions:
Concomitant use with other CNS active drugs should be approached with caution. There is one report suggesting that the concomitant use of Desyrel® (trazodone) and BuSpar may have caused 3- to 6-fold elevations on SGPT (ALT) in a few patients. In a similar study, attempting to replicate this finding, no interactive effect on hepatic transaminases was identified. Buspirone does not displace tightly bound drugs like phenytoin, propranolol and warfarin from serum proteins, but may displace less firmly bound drugs like digoxin. (See WARNINGS)

Carcinogenesis, Mutagenesis, Impairment of Fertility:
No evidence of carcinogenic potential was observed in rats or mice; buspirone did not induce point mutations, nor was DNA damage observed; chromosomal aberrations or abnormalities did not occur.

Pregnancy:
Teratogenic Effects:
Pregnancy Category B: Should be used during pregnancy only if clearly needed.

Nursing Mothers:
Administration to nursing women should be avoided if clinically possible.

Pediatric Use:
The safety and effectiveness have not been determined in individuals below 18 years of age.

Use in the Elderly:
No unusual adverse age-related phenomena have been identified in elderly patients.

Use in Patients with Impaired Hepatic or Renal Function:
Since buspirone is metabolized by the liver and excreted by the kidneys, its administration to patients with severe hepatic or renal impairment cannot be recommended.

ADVERSE REACTIONS (See also Precautions):
Commonly Observed:
The more commonly observed untoward events associated with the use of BuSpar not seen at an equivalent incidence among placebo-treated patients include dizziness, nausea, headache, nervousness, light-headedness and excitement.

Associated with Discontinuation of Treatment:
The more common events causing discontinuation included central nervous system disturbances (3.4%)—primarily dizziness, insomnia, nervousness, drowsiness, and light-headed feeling; gastrointestinal disturbances (1.2%)—primarily nausea; and miscellaneous disturbances (1.1%)—primarily headache and fatigue. In addition, 3.4% of patients had multiple complaints, none of which could be characterized as primary.

Incidence in Controlled Clinical Trials:
Adverse events that occurred at a frequency of 1% or more among 477 patients who received buspirone in four-week, controlled trials: **Cardiovascular:** tachycardia/palpitations 1%. **CNS:** dizziness 12%, drowsiness 10%, nervousness 5%, insomnia 3%, light-headedness 3%, decreased concentration 2%, excitement 2%, anger/hostility 2%, confusion 2%, depression 2%. **EENT:** blurred vision 2%. **Gastrointestinal:** nausea 8%, dry mouth 3%, abdominal/gastric distress 2%, diarrhea 2%, constipation 1%, vomiting 1%. **Musculoskeletal:** musculoskeletal aches/pains 1%. **Neurological:** numbness 2%, paresthesia 1%, incoordination 1%, tremor 1%. **Skin:** skin rash 1%. **Miscellaneous:** headache 6%, fatigue 4%, weakness 2%, sweating/clamminess 1%.

Other Events Observed During the Entire Pre-Marketing Evaluation:
The following list includes all other adverse events reasonably associated with the use of buspirone in approximately 3000 subjects who took multiple doses of the drug under various conditions in well-controlled studies as well as open and uncontrolled clinical settings. The relative frequency of these adverse events is defined as follows: Frequent are those occurring in at least 1/100 patients; infrequent are those occurring in 1/100 to 1/1000 patients; and rare are those occurring in less than 1/1000 patients. **Cardiovascular:** Frequent was nonspecific chest pain; infrequent were syncope, hypotension and hypertension; rare were cerebrovascular accident, congestive heart failure, myocardial infarction, cardiomyopathy and bradycardia. **Central Nervous System:** Frequent were dream disturbances; infrequent were depersonalization, dysphoria, noise intolerance, euphoria, akathisia, fearfulness, loss of interest, dissociative reaction, hallucinations, suicidal ideation and seizures; rare were feelings of claustrophobia, cold intolerance, stupor, and slurred speech and psychosis. **EENT:** Frequent were tinnitus, sore throat and nasal congestion. Infrequent were redness and itching of the eyes, altered taste, altered smell, and conjunctivitis; rare were inner ear abnormality, eye pain, photophobia, and pressure on eyes. **Endocrine:** Rare were galactorrhea and thyroid abnormality. **Gastrointestinal:** Infrequent were flatulence, anorexia, increased appetite, salivation, irritable colon and rectal bleeding; rare was burning of the tongue. **Genitourinary:** Infrequent were urinary frequency, urinary hesitancy, menstrual irregularity and spotting, and dysuria; rare were amenorrhea, pelvic inflammatory disease, enuresis and nocturia. **Musculoskeletal:** Infrequent were muscle cramps, muscle spasms, rigid/stiff muscles, and arthralgias. **Neurological:** Infrequent were involuntary movements and slowed reaction time; rare was muscle weakness. **Respiratory:** Infrequent were hyperventilation, shortness of breath and chest congestion; rare was epistaxis. **Sexual Function:** Infrequent were decreased or increased libido; rare were delayed ejaculation and impotence. **Skin:** Infrequent were edema, pruritus, flushing, easy bruising, hair loss, dry skin, facial edema and blisters; rare were acne and thinning of nails. **Clinical Laboratory:** Infrequent were increases in hepatic aminotransferases (SGOT, SGPT); rare were eosinophilia, leukopenia and thrombocytopenia. **Miscellaneous:** Infrequent were weight gain, fever, roaring sensation in the head, weight loss and malaise; rare were alcohol abuse, bleeding disturbance, loss of voice and hiccoughs.

DRUG ABUSE AND DEPENDENCE:
Controlled Substance Class:
BuSpar is not a controlled substance.

Physical and Psychological Dependence:
Buspirone has shown no potential for abuse or diversion and there is no evidence that it causes tolerance, or either physical or psychological dependence. However, since it is difficult to predict from experiments the extent to which a CNS active drug will be misused, diverted and/or abused once marketed, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of buspirone misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE:
Signs and Symptoms:
No deaths have been reported in humans either with deliberate or accidental overdosage. At doses approaching 375 mg/day, the following symptoms were observed: nausea, vomiting, dizziness, drowsiness, miosis, and gastric distress.

Recommended Overdose Treatment:
General symptomatic and supportive measures should be used along with immediate gastric lavage. No specific antidote is known and dialyzability of buspirone has not been determined.

For complete details, see Prescribing Information or consult your Mead Johnson Pharmaceutical Division Representative.

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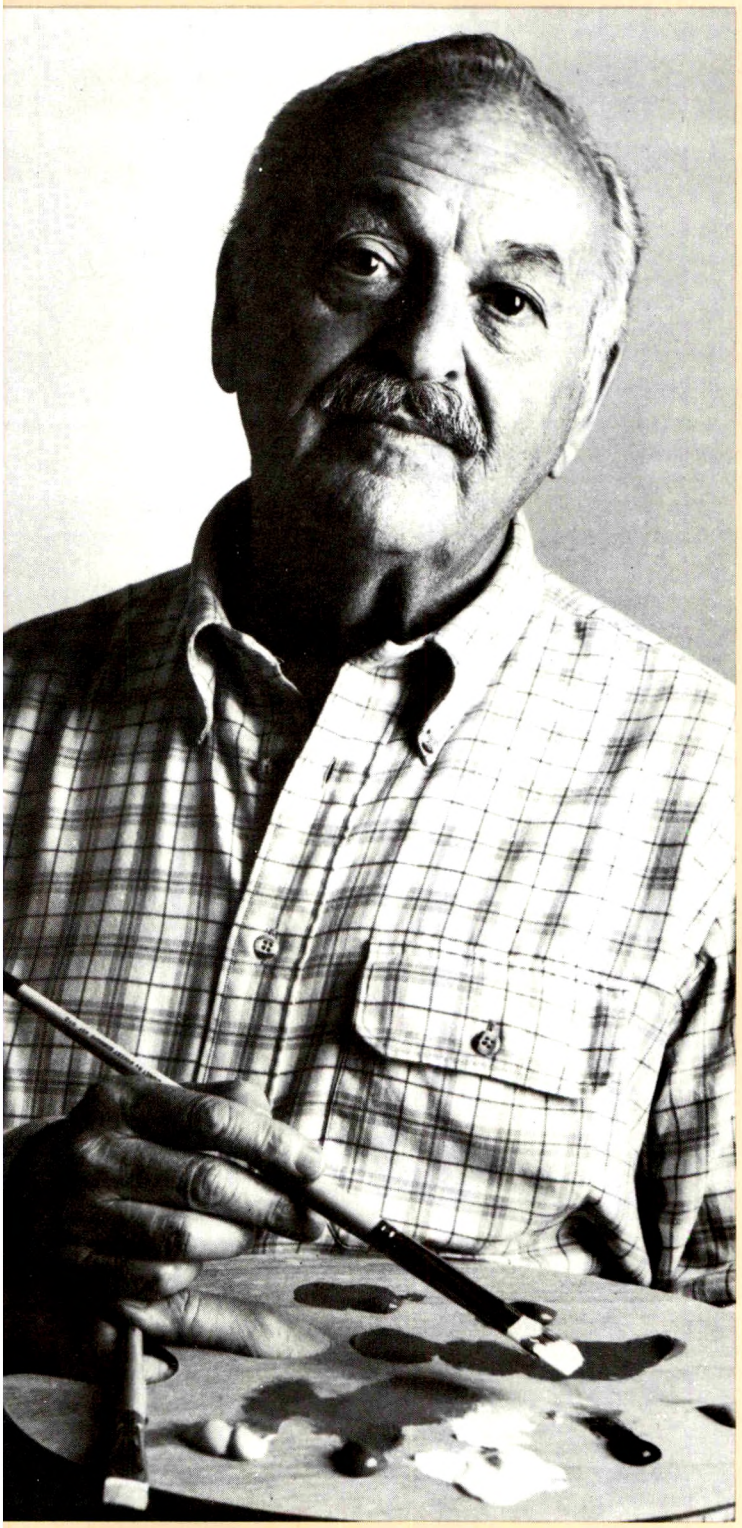
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INDICATIONS: MOBAN is indicated for the management of the manifestations of psychotic disorders. The antipsychotic efficacy of MOBAN was established in clinical studies which enrolled newly hospitalized and chronically hospitalized, acutely ill, schizophrenic patients as subjects.

CONTRAINDICATIONS: Severe central nervous system depression, comatose states from any cause, and in patients with known hypersensitivity to the drug.

WARNINGS: Tardive Dyskinesia—This syndrome (potentially irreversible, involuntary, dyskinetic movements) may develop in patients treated with neuroleptic (antipsychotic) drugs. Prevalence appears highest among the elderly, especially women; it is impossible to predict which patients are likely to develop the syndrome. Both risk of syndrome development and likelihood of its becoming irreversible are believed to increase with duration of treatment and total cumulative dose; the syndrome can develop after brief treatment periods at low doses. There is no known treatment; partial or complete remission may occur if neuroleptic treatment is withdrawn. Neuroleptic treatment may supress or partially supress signs and symptoms of the syndrome and thereby mask the underlying disease process. Effect of symptomatic supression upon long-term course of the syndrome is unknown. Prescribe neuroleptics in a manner most likely to minimize the occurrence of tardive dyskinesia. Reserve chronic neuroleptic treatment for patients suffering from a chronic illness that is known to respond to neuroleptic drugs and for whom alternative treatments are not available or appropriate. In those requiring chronic treatment the smallest dose and shortest duration of treatment producing satisfactory clinical response should be sought. Need for treatment should be reassessed periodically. Consider discontinuing treatment if signs and symptoms of tardive dyskinesia appear; some patients may require treatment despite presence of the syndrome.

Usage in Pregnancy: Studies in pregnant patients have not been carried out. Animal reproductive studies have not demonstrated a teratogenic potential. Anticipated benefits must be weighed against the unknown risks to the fetus if used in pregnant patients.

Nursing Mothers: Data are not available on the content of MOBAN in the milk of nursing mothers.

Usage in Children: Use of MOBAN in children below the age of twelve years is not recommended because safe and effective conditions for its usage have not been established. MOBAN has not been shown effective in the management of behavioral complications in patients with mental retardation.

Sulfites Sensitivity: MOBAN Concentrate contains sodium metabisulfite, a sulfite that may cause allergic-type reactions (e.g. hives, itching, wheezing, anaphylaxis) in certain susceptible persons. Although the overall prevalence of sulfite sensitivity in the general population is probably low, it is seen more frequently in asthmatics or in atopic nonasthmatic persons.

PRECAUTIONS: Some patients may note drowsiness initially; advise against activities requiring mental alertness until response to the drug has been established. Increased activity has been noted in patients receiving MOBAN. Caution should be exercised where increased activity may be harmful. MOBAN does not lower the seizure threshold in experimental animals to the degree noted with more sedating antipsychotic drugs; in humans convulsive seizures have been reported in a few instances. This tablet preparation contains calcium sulfate as an excipient; calcium ions may interfere with the absorption of preparations containing phenytoin sodium and tetracyclines. MOBAN has an antiemetic effect in animals. A similar effect may occur in humans and may obscure signs of intestinal obstruction or brain tumor. Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis; the available evidence is considered too limited to be conclusive at this time.

ADVERSE REACTIONS: CNS EFFECTS: Most frequently occurring effect is initial drowsiness that generally subsides with continued usage or lowering of the dose. Noted less frequently were depression, hyperactivity and euphoria.

Neurological—Extrapyramidal Reactions noted below may occur in susceptible individuals; usually reversible with appropriate management.

Akathisia: Motor restlessness may occur early.

Parkinson Syndrome: Akinesia, characterized by rigidity, immobility and reduction of voluntary movements and tremor, have been observed. Occurrence is less frequent than akathisia.

Dystonic Syndrome: Prolonged abnormal contractions of muscle groups occur infrequently. Symptoms may be managed by the addition of a synthetic antiparkinson agent (other than L-dopa), small doses of sedative drugs, and/or reduction in dosage.

Tardive Dyskinesia: Persistent and sometimes irreversible. See preceeding paragraph under "Warnings."

Autonomic Nervous System: Occasional blurring of vision, tachycardia, nausea, dry mouth and salivation. Urinary retention and constipation may occur, particularly if anticholinergic drugs are used to treat extrapyramidal symptoms.

Laboratory Tests: Rare reports of leucopenia and leucocytosis; treatment with MOBAN may continue if clinical symptoms are absent. Alterations of blood glucose, liver function tests, BUN, and red blood cells have not been considered clinically significant.

Metabolic and Endocrine Effects: Alteration of thyroid function has not been significant. Amenorrhea has been reported infrequently. Resumption of menses in previously amenorrheic women has been reported. Initially heavy menses may occur. Galactorrhea and gynecomastia have been reported infrequently. Increase in libido has been noted in some patients. Impotence has not been reported. Although both weight gain and weight loss have been in the direction of normal or ideal weight, excessive weight gain has not occurred with MOBAN.

Hepatic Effects: There have been rare reports of clinically significant alterations in liver function in association with MOBAN use.

Cardiovascular: Rare, transient, non-specific T wave changes have been reported on EKG. Association with a clinical syndrome has not been established. Rarely has significant hypotension been reported.

Ophthalmological: Lens opacities and pigmentary retinopathy have not been reported. In some patients phenothiazine-induced lenticular opacities have resolved following discontinuation of the phenothiazine while continuing therapy with MOBAN.

Skin: Early non-specific skin rash, probably of allergic origin, has occasionally been reported. Skin pigmentation has not been seen with MOBAN usage alone. MOBAN has certain pharmacological similarities to other antipsychotic agents. Because adverse reactions are often extensions of the pharmacological activity of a drug, all of the known pharmacological effects associated with other antipsychotic drugs should be kept in mind when MOBAN is used. Upon abrupt withdrawal after prolonged high dosage an abstinence syndrome has not been noted.

DOSAGE: Initial and maintenance doses of MOBAN should be individualized. See full prescribing information.

OVERDOSAGE: For information on signs and symptoms, and treatment of overdosage, see full prescribing information.

HOW SUPPLIED: Tablets: 5 mg, 10 mg, 25 mg, 50 mg and 100 mg in bottles of 100.

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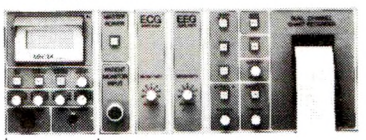
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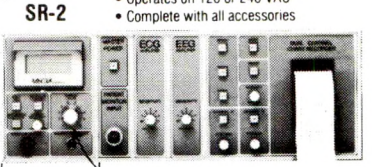


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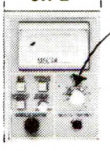
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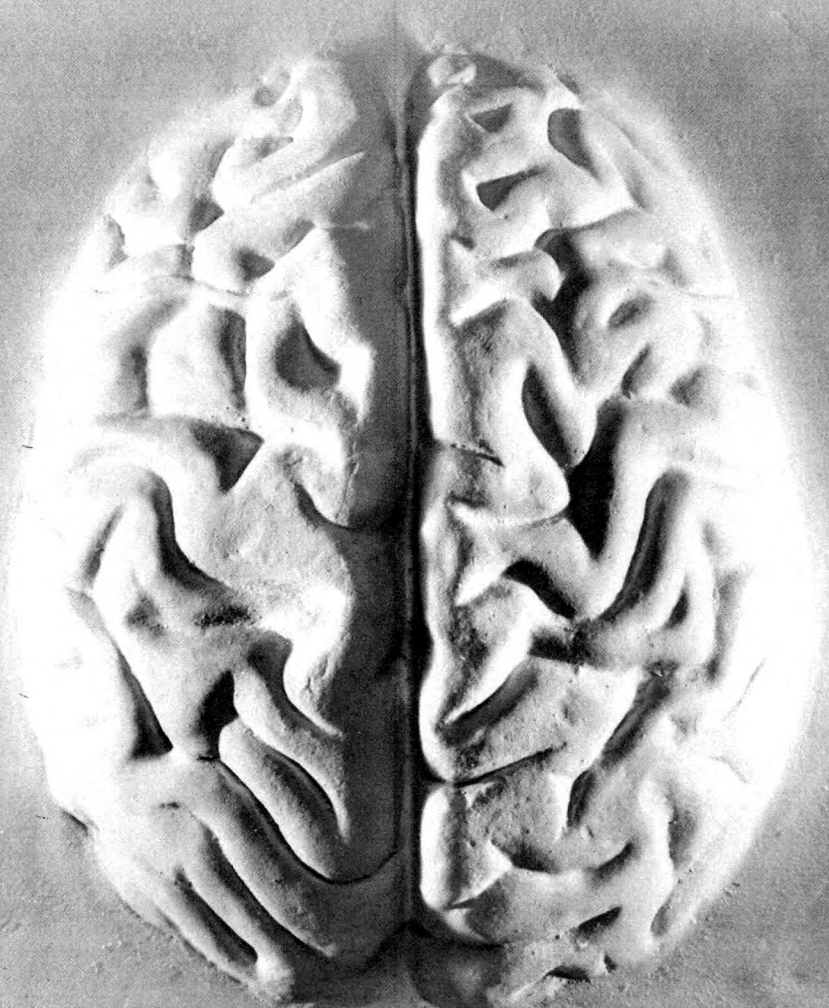


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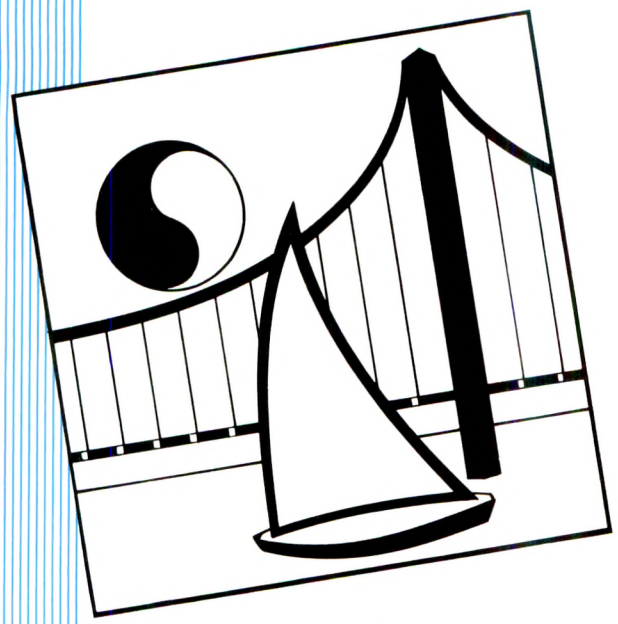
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Indications: Management of anxiety disorders; short-term relief of anxiety symptoms, acute alcohol withdrawal symptoms, preoperative apprehension and anxiety. Usually not required for anxiety or tension associated with stress of everyday life. Efficacy beyond four months not established by systematic clinical studies. Periodic reassessment of therapy recommended.
Contraindications: Known hypersensitivity to the drug.
Warnings: Warn patients that mental and/or physical abilities required for tasks such as driving or operating machinery may be impaired, as may be mental alertness in children, and that concomitant use with alcohol or CNS depressants may have an additive effect. Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage. Withdrawal symptoms (including convulsions) reported after abrupt cessation of extended use of excessive doses are similar to those seen with barbiturates. Milder symptoms reported infrequently when continuous therapy is abruptly ended. Avoid abrupt discontinuation; gradually taper dosage.
***Usage in Pregnancy:* Use of minor tranquilizers during the first trimester should almost always be avoided because of increased risk of congenital malformations as suggested in several studies. Consider possibility of pregnancy when instituting therapy; advise patients to discuss therapy if they intend to or do become pregnant.**
Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically. Due to isolated reports of exacerbation, use with caution in patients with porphyria.
Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.
Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral—Adults:* Mild and moderate anxiety disorders and symptoms, 5 or 10 mg *t.i.d.* or *q.i.d.*; severe states, 20 or 25 mg *t.i.d.* or *q.i.d. Geriatric patients:* 5 mg *b.i.d.* to *q.i.d.* (See Precautions.)
Supplied: Librium® (chlordiazepoxide HCl/Roche) *Capsules,* 5 mg, 10 mg and 25 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in boxes of 4 reverse-numbered cards of 25, and in boxes containing 10 strips of 10. Libritabs® (chlordiazepoxide/Roche) *Tablets,* 5 mg and 10 mg—bottles of 100 and 500; 25 mg—bottles of 100. With respect to clinical activity, capsules and tablets are indistinguishable.

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Please see adjacent page for summary of product information.

Calendar

For free listing of your organization's official annual or regional meeting, please send us the following information: sponsor, location, inclusive dates, type and number of continuing education credits (if available), and the name, address, and telephone number of the person or group to contact for more information. All notices and changes must be received no later than 120 days before the first day of the month of desired publication and should be addressed to Calendar, American Journal of Psychiatry, *1400 K St., N.W., Washington, DC 20005. Because of space limitations, only listings of meetings of the greatest interest to* Journal *readers will be included.*

AUGUST

August 2–6, annual conference, African Psychiatric Association, Harare, Zimbabwe. Contact Godfrey Huggins, School of Medicine, P.O. Box A 178, Avondale, Harare, Zimbabwe.

August 3–5, annual convention, American Hospital Association, Philadelphia. Contact H. Joseph Curl, Executive Vice-President, 840 North Lake Shore Dr., Chicago, IL 60611; 312-280-6000.

August 6–13, annual meeting, American Bar Association, San Francisco. Contact Thomas H. Gonser, Esq., Executive Director, 750 North Lake Shore Dr., Chicago, IL 60611; 312-988-5130.

August 9–13, annual meeting, American Institute of Biological Sciences, Columbus, Ohio. Contact Dr. Charles M. Chambers, Executive Director, 730 11th St., N.W., Washington, DC 20001-4584; 202-628-1500.

August 9–14, XIV Annual Symposium, Neuropsychiatric Aspects of Sociopathy, Kamuela, Hawaii. Contact Teresa Santana, S.C.N.P.I., 6794 La Jolla Blvd., La Jolla, CA 92037; 619-454-2102, 800-423-9521.

August 12–16, annual conference, American Association for Partial Hospitalization, Boston. Contact Joan Fridberg, 1221 Massachusetts Ave., N.W., Suite B, Washington, DC 20005; 202-347-1649.

August 17–21, annual meeting, American Sociological Association, Chicago. Contact Jen L. Suter, Meetings and Marketing Manager, ASA, 1722 N Street, N.W., Washington, DC 20036; 202-833-3410.

August 23–28, annual meeting, Canadian Medical Association, Charlottetown, Canada. Contact B.E. Freamo, Secretary-General, P.O. Box 8650, Ottawa, Ontario K1G 0G8, Canada; 613-731-9331.

August 28–31, Third Congress of the International Psychogeriatric Association, Chicago. Contact Congress Coordinator, Northwestern Memorial Hospital, Institute of Psychiatry, Older Adult Program, 259 East Erie—#448, Chicago, IL 60611; 312-908-1248.

August 28–September 1, annual meeting, American Psychological Association, New York. Contact Leonard D. Goodstein, Ph.D., Executive Officer, 1200 17th St., N.W., Washington, DC 20036; 202-955-7600.

August 30–September 1, annual meeting, International College of Psychosomatic Medicine, Sydney, Australia. Contact Professor Carins Aitken, M.D., Executive Director, Rehabilitation Studies Unit, Princess Margaret Rose Hospital, Edinburgh, EH10 7ED, Scotland.

SEPTEMBER

September 4–5, fall meeting, American Association for Social Psychiatry, New Orleans. Contact Carolyn B. Robinowitz, M.D., Secretary-Treasurer, AASP, 1400 K St., N.W., Washington, DC 20005; 202-682-6130.

September 9–12, annual meeting, National Association of Social Workers, New Orleans. Contact Mark G. Battle, A.C.S.W., Executive Director, 7981 Eastern Ave., Silver Spring, MD 20910; 301-565-0333.

September 9–13, Fall Components Meeting, American Psychiatric Association, Washington, D.C.

September 9–13, 2nd International Symposium on Premenstrual, Postpartum and Menopausal Mood Disorders, Kiawah Island, S.C. Contact University of Medicine and Dentistry of New Jersey, Office of Continuing Education, 675 Hoes Ln., Piscataway, NJ 08854-5635; 201-463-4707.

September 11–13, annual conference, Canadian Art Therapy Association, Vancouver, Canada. Contact CATA, Conference Committee, 216 St. Clair Avenue West, Toronto, Ontario M4V 1R2, Canada; 416-921-4374.

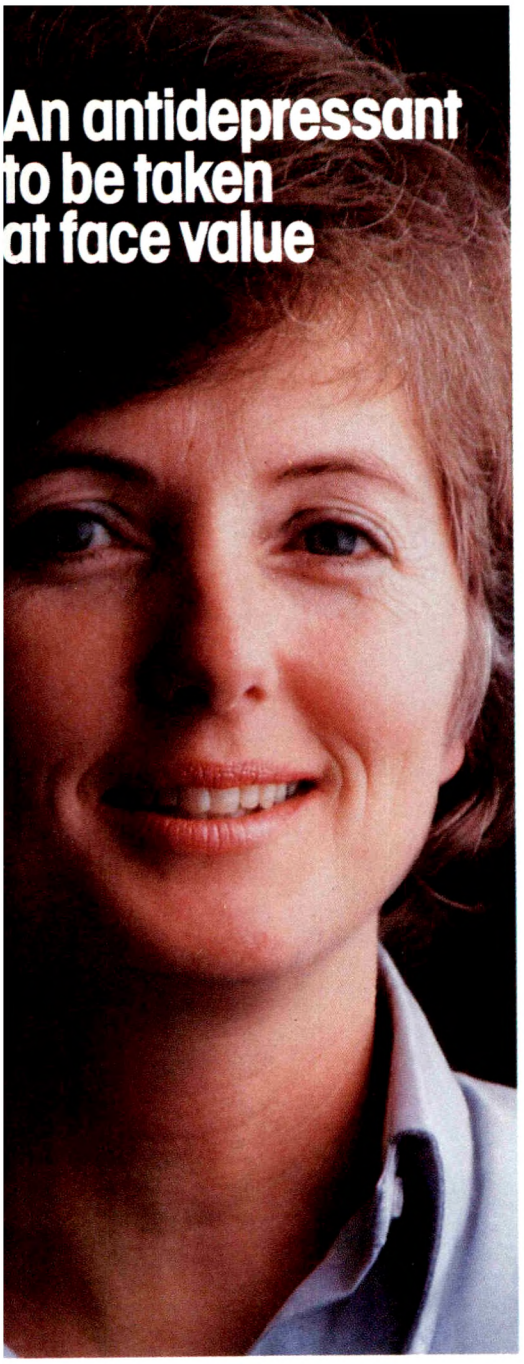
September 11–15, annual meeting, Royal College of Physicians and Surgeons of Canada, Winnipeg, Canada. Contact Dr. J.H. Darragh, Executive Director, 74 Stanley Ave., Ottawa, Ontario K1M 1P4, Canada; 613-746-8177.

September 13–15, annual meeting, Canadian Academy of Child Psychiatry, London, Ontario. Contact J.H. Beitchman, M.D., Program Chairman, CACP, Clarke Institute of Psychiatry, 250 College St., Toronto, Ontario M5T 1R8, Canada.

September 14–17, annual meeting, American Academy of Family Physicians, San Francisco. Contact Robert Graham, M.D., Executive Vice-President, 1740 West 92nd St., Kansas City, MO 64114; 816-333-9700.

September 16–18, annual meeting, Canadian Psychiatric Association, London, Ontario. Contact Lea C. Metivier,

(Continued on page A40)



PAMELOR®
(nortriptyline HCl)

The active metabolite of amitriptyline

All the efficacy of amitriptyline and a favorable side effect profile

Because of anticholinergic activity, PAMELOR (nortriptyline HCl) should be used with caution in patients who have glaucoma or a history of urinary retention.

Contraindications: 1) Concurrent use with a monoamine oxidase (MAO) inhibitor, since hyperpyretic crises, severe convulsions, and fatalities have occurred when similar tricyclic antidepressants were used in such combinations; MAO inhibitors should be discontinued for at least two weeks before treatment with Pamelor® (nortriptyline HCl) is started. 2) Hypersensitivity to Pamelor (nortriptyline HCl), cross-sensitivity with other dibenzazepines is a possibility. 3) The acute recovery period after myocardial infarction.

Warnings: Give only under close supervision to patients with cardiovascular disease, because of the tendency of the drug to produce sinus tachycardia and to prolong conduction time; myocardial infarction, arrhythmia, and strokes have occurred. The antihypertensive action of guanethidine and similar agents may be blocked. Because of its anticholinergic activity, nortriptyline should be used with great caution in patients who have glaucoma or a history of urinary retention. Patients with a history of seizures should be followed closely, since nortriptyline is known to lower the convulsive threshold. Great care is required in hyperthyroid patients or those receiving thyroid medication, since cardiac arrhythmias may develop. Nortriptyline may impair the mental and/or physical abilities required for the performance of hazardous tasks, such as operating machinery or driving a car; therefore, the patient should be warned accordingly. Excessive consumption of alcohol may have a potentiating effect, which may lead to the danger of increased suicidal attempts or overdosage, especially in patients with histories of emotional disturbances or suicidal ideation.

Use in Pregnancy—Safe use during pregnancy and lactation has not been established; therefore, in pregnant patients, nursing mothers, or women of childbearing potential, the potential benefits must be weighed against the possible hazards.

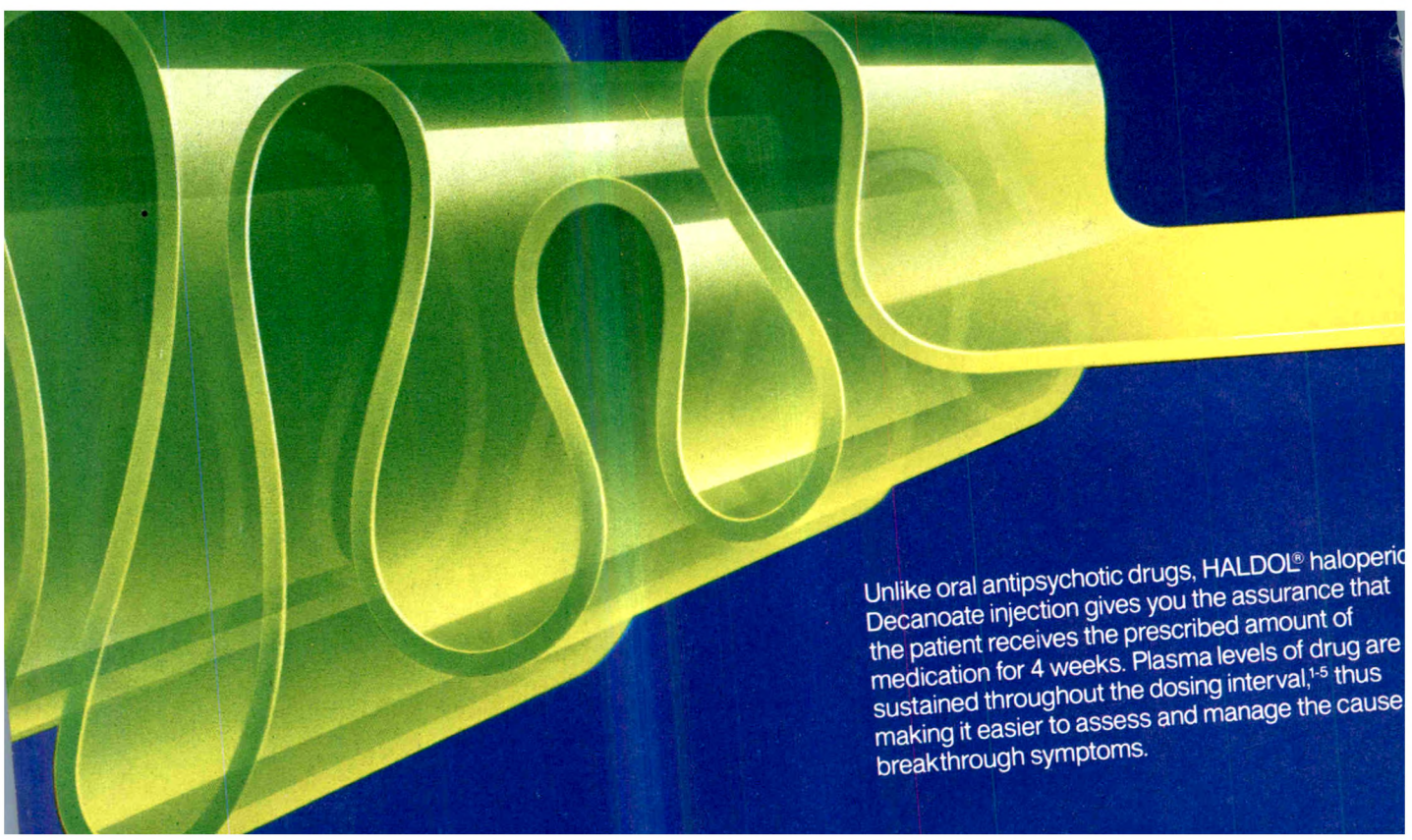
Use in Children—Not recommended for use in children, since safety and effectiveness in the pediatric age group have not been established.

Precautions: Use in schizophrenic patients may result in an exacerbation of the psychosis or may activate latent schizophrenic symptoms; in overactive or agitated patients, increased anxiety and agitation may occur; in manic-depressive patients, symptoms of the manic phase may emerge. Administration of reserpine during therapy with a tricyclic antidepressant has been shown to produce a "stimulating" effect in some depressed patients. Troublesome patient hostility may be aroused. Epileptiform seizures may accompany administration. Close supervision and careful adjustment of dosage are required when used with other anticholinergic drugs and sympathomimetic drugs. Concurrent administration of cimetidine can produce clinically significant increases in the plasma concentrations of the tricyclic antidepressant. Patients should be informed that the response to alcohol may be exaggerated. When essential, may be administered with electroconvulsive therapy, although the hazards may be increased. Discontinue the drug for several days, if possible, prior to elective surgery. The possibility of a suicidal attempt by a depressed patient remains after the initiation of treatment; in this regard, it is important that the least possible quantity of drug be dispensed at any given time. Both elevation and lowering of blood sugar levels have been reported.

Adverse Reactions: *Cardiovascular*—Hypotension, hypertension, tachycardia, palpitation, myocardial infarction, arrhythmias, heart block, stroke. *Psychiatric*—Confusional states (especially in the elderly) with hallucinations, disorientation, delusions; anxiety, restlessness, agitation; insomnia, panic, nightmares; hypomania, exacerbation of psychosis. *Neurologic*—Numbness, tingling, paresthesias of extremities; incoordination, ataxia, tremors; peripheral neuropathy; extrapyramidal symptoms; seizures, alteration in EEG patterns; tinnitus. *Anticholinergic*—Dry mouth and, rarely, associated sublingual adenitis; blurred vision, disturbance of accommodation, mydriasis; constipation, paralytic ileus; urinary retention, delayed micturition, dilation of the urinary tract. *Allergic*—Skin rash, petechiae, urticaria, itching, photosensitization (avoid excessive exposure to sunlight); edema (general or of face and tongue), drug fever, cross-sensitivity with other tricyclic drugs. *Hematologic*—Bone-marrow depression, including agranulocytosis; eosinophilia; purpura, thrombocytopenia. *Gastrointestinal*—Nausea and vomiting, anorexia, epigastric distress, diarrhea, peculiar taste, stomatitis, abdominal cramps, black-tongue. *Endocrine*—Gynecomastia in the male, breast enlargement and galactorrhea in the female; increased or decreased libido, impotence; testicular swelling; elevation or depression of blood sugar levels; syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Other*—Jaundice (simulating obstructive), altered liver function; weight gain or loss; perspiration; flushing; urinary frequency, nocturia; drowsiness, dizziness, weakness, fatigue; headache; parotid swelling; alopecia. *Withdrawal Symptoms*—Though these are not indicative of addiction, abrupt cessation of treatment after prolonged therapy may produce nausea, headache, and malaise.

Overdosage: Toxic overdosage may result in confusion, restlessness, agitation, vomiting, hyperpyrexia, muscle rigidity, hyperactive reflexes, tachycardia, ECG evidence of impaired conduction, shock, congestive heart failure, stupor, coma, and CNS stimulation with convulsions followed by respiratory depression. Deaths have occurred with drugs of this class. No specific antidote is known; general supportive measures are indicated, with gastric lavage. [PAM-Z13—7 15 86]

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Unlike oral antipsychotic drugs, HALDOL® haloperic
Decanoate injection gives you the assurance that
the patient receives the prescribed amount of
medication for 4 weeks. Plasma levels of drug are
sustained throughout the dosing interval,[1-5] thus
making it easier to assess and manage the cause
breakthrough symptoms.

Sustained drug levels with a single monthly dose

HALDOL® DECANOATE
(HALOPERIDOL) INJECTION

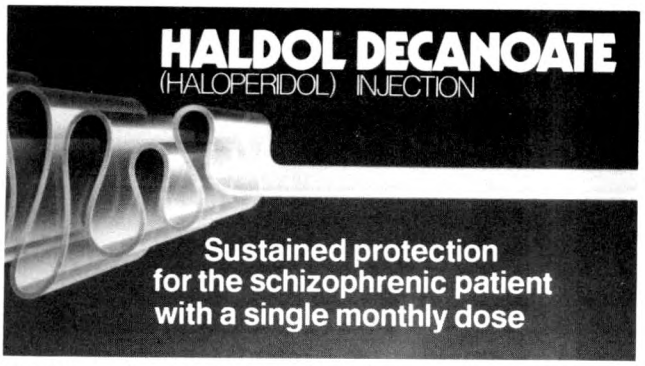
the therapeutic constant in schizophrenia

Pharmacokinetic profile facilitates monthly dosing

Smooth, steady drug delivery has been shown to

Offers sustained protection against schizophrenic relapse

Dependable delivery with HALDOL Decanoate helps



The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5 and 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of in rats at doses up to 20 times the usual dail patients. In female mice at 5 and 20 times the resistant patients, there was a statistically si neoplasia and total tumor incidence; at 20 ti statistically significant increase in pituitary statistically significant differences in inciden types were noted.

Antipsychotic drugs elevate prolactin level administration. Tissue culture experiments in human breast cancers are prolactin depe importance if the prescription of these drug previously detected breast cancer. Althoug amenorrhea, gynecomastia, and impotence ficance of elevated serum prolactin levels is ur in mammary neoplasms has been found in r antipsychotic drugs. Neither clinical studies to date, however, have shown an associatic these drugs and mammary tumorigenesis: th limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category likely to become pregnant has not been es justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nurs

Pediatric Use: Controlled trials to establ intramuscular administration in children have

Adverse Reactions: Adverse reactions follc (haloperidol) Decanoate are those of HALDC mulated with HALDOL, the adverse reaction well as for HALDOL Decanoate. As with all reactions have been reported with HALDOL D

CNS Effects: Extrapyramidal Reactions—N tions have been reported frequently, often d Generally they involved Parkinson-like sympt usually mild to moderately severe and usuall cular reactions (motor restlessness, dystor hyperreflexia, opisthotonos, oculogyric crise quently, but were often more severe. Severe reported at relatively low doses. Generally, ex lated since they occur at relatively high doses when the dose is reduced. Antiparkinson extrapyramidal reactions have been report discontinued in such cases. *Withdrawal Er* discontinuation of short-term antipsychotic t ever, some patients on maintenance treatm signs after abrupt withdrawal. In certain cas "Tardive Dyskinesia" except for duration. It is u will reduce the occurrence of these signs, b HALDOL should be gradually withdrawn. *Tar* chotic agents HALDOL has been associated dyskinesia, a syndrome consisting of potentia movements, may appear in some patients on drug therapy has been discontinued. The ri patients on high-dose therapy, especially fer and in some patients appear irreversible. rhythmical involuntary movements of tongue, tongue, puffing of cheeks, puckering of mout these may be accompanied by involuntary mo There is no known effective treatment for tard usually do not alleviate the symptoms of thi antipsychotic agents be discontinued if the necessary to reinstitute treatment, or increase a different antipsychotic agent, this syndrome that fine vermicular movement of the tongu dyskinesia and if the medication is stopped a develop. *Other CNS Effects:* Insomnia, restle drowsiness, depression, lethargy, headache zures, and exacerbation of psychotic symp catatonic-like behavioral states which may be treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic Malignant Sy drugs, a symptom complex sometimes re syndrome (NMS) has been reported. Cardina muscle rigidity, altered mental status (includi autonomic instability (irregular pulse or blo include elevated creatinine phosphokinase, n acute renal failure. NMS is potentially fatal, re ment and immediate discontinuation of antips heat stroke, not associated with the above reported. *Cardiovascular Effects:* Tachycardia, changes. *Hematologic Effects:* Reports of mi leukocytosis, minimal decreases in red blood toward lymphomonocytosis; agranulocytosis tion with other medication. *Liver Effects:* Imp *Dermatologic Reactions:* Maculopapular and a photosensitivity, loss of hair. *Endocrine Disord* mastalgia, menstrual irregularities, gynecom hyperglycemia, hypoglycemia and hyponatre exia, constipation, diarrhea, hypersalivation, *Autonomic Reactions:* Dry mouth, blurred visio priapism. *Respiratory Effects:* Laryngospasm, of respiration. *Special Senses:* Cataracts, re *Other:* Cases of sudden and unexpected deat with the administration of HALDOL. The nature to determine definitively what role, if any, HA reported cases. The possibility that HALDOL excluded, but it is to be kept in mind that sudde in psychotic patients when they go untreated antipsychotic drugs.

IMPORTANT: Full directions for use sho HALDOL Decanoate is administered or pres For information on symptoms and treatmen ing information.

The short-acting HALDOL injectable form i psychotic patients with moderately severe to ve

McNEIL

Her doctor helped her save a lot by prescribing Sinequan...

her family life

In the treatment of depression, 18 invaluable years of unsurpassed effectiveness and safety. The very picture of proven performance.

SINEQUAN®

(doxepin HCl)

150-mg, * 100-mg, 75-mg, 50-mg, 25-mg, and 10-mg CAPSULES and ORAL CONCENTRATE 10-mg/ml, 120-ml (4-oz) bottles

Helps save what matters most

...ce therapy only and is not recommended for ...

...pin HCl) prescribing information

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BRIEF SUMMARY
SINEQUAN® (doxepin HCl) Capsules/Oral Concentrate
Indications. SINEQUAN is recommended for the treatment of:
1. Psychoneurotic patients with depression and/or anxiety.
2. Depression and/or anxiety associated with alcoholism (not to be taken concomitantly with alcohol).
3. Depression and/or anxiety associated with organic disease (the possibility of drug interaction should be considered if the patient is receiving other drugs concomitantly).
4. Psychotic depressive disorders with associated anxiety including involutional depression and manic-depressive disorders.

The target symptoms of psychoneurosis that respond particularly well to SINEQUAN include anxiety, tension, depression, somatic symptoms and concerns, sleep disturbances, guilt, lack of energy, fear, apprehension and worry.

Clinical experience has shown that SINEQUAN is safe and well tolerated even in the elderly patient. Owing to lack of clinical experience in the pediatric population, SINEQUAN is not recommended for use in children under 12 years of age.

Contraindications. SINEQUAN is contraindicated in individuals who have shown hypersensitivity to the drug. Possibility of cross sensitivity with other dibenzoxepines should be kept in mind.

SINEQUAN is contraindicated in patients with glaucoma or a tendency to urinary retention. These disorders should be ruled out, particularly in older patients.

Warnings. The once-a-day dosage regimen of SINEQUAN in patients with intercurrent illness or patients taking other medications should be carefully adjusted. This is especially important in patients receiving other medications with anticholinergic effects.

Usage in Geriatrics: The use of SINEQUAN on a once-a-day dosage regimen in geriatric patients should be adjusted carefully based on the patient's condition.

Usage in Pregnancy: Reproduction studies have been performed in rats, rabbits, monkeys and dogs and there was no evidence of harm to the animal fetus. The relevance to humans is not known. Since there is no experience in pregnant women who have received this drug, safety in pregnancy has not been established. There are no data with respect to the secretion of the drug in human milk and its effect on the nursing infant.

Usage in Children: The use of SINEQUAN in children under 12 years of age is not recommended because safe conditions for its use have not been established.

MAO Inhibitors: Serious side effects and even death have been reported following the concomitant use of certain drugs with MAO inhibitors. Therefore, MAO inhibitors should be discontinued at least two weeks prior to the cautious initiation of therapy with SINEQUAN. The exact length of time may vary and is dependent upon the particular MAO inhibitor being used, the length of time it has been administered, and the dosage involved.

Usage with Alcohol: It should be borne in mind that alcohol ingestion may increase the danger inherent in any intentional or unintentional SINEQUAN overdosage. This is especially important in patients who may use alcohol excessively.

Precautions. Since drowsiness may occur with the use of this drug, patients should be warned of the possibility and cautioned against driving a car or operating dangerous machinery while taking the drug. Patients should also be cautioned that their response to alcohol may be potentiated.

Since suicide is an inherent risk in any depressed patient and may remain so until significant improvement has occurred, patients should be closely supervised during the early course of therapy. Prescriptions should be written for the smallest feasible amount.

Should increased symptoms of psychosis or shift to manic symptomatology occur, it may be necessary to reduce dosage or add a major tranquilizer to the dosage regimen.

Adverse Reactions. NOTE: Some of the adverse reactions noted below have not been specifically reported with SINEQUAN use. However, due to the close pharmacological similarities among the tricyclics, the reactions should be considered when prescribing SINEQUAN.

Anticholinergic Effects: Dry mouth, blurred vision, constipation, and urinary retention have been reported. If they do not subside with continued therapy, or become severe, it may be necessary to reduce the dosage.

Central Nervous System Effects: Drowsiness is the most commonly noticed side effect. This tends to disappear as therapy is continued. Other infrequently reported CNS side effects are confusion, disorientation, hallucinations, numbness, paresthesias, ataxia, and extrapyramidal symptoms and seizures.

Cardiovascular: Cardiovascular effects including hypotension and tachycardia have been reported occasionally.

Allergic: Skin rash, edema, photosensitization, and pruritus have occasionally occurred

Hematologic: Eosinophilia has been reported in a few patients. There have been occasional reports of bone marrow depression manifesting as agranulocytosis, leukopenia, thrombocytopenia, and purpura.

Gastrointestinal: Nausea, vomiting, indigestion, taste disturbances, diarrhea, anorexia, and aphthous stomatitis have been reported. (See anticholinergic effects.)

Endocrine: Raised or lowered libido, testicular swelling, gynecomastia in males, enlargement of breasts and galactorrhea in the female, raising or lowering of blood sugar levels, and syndrome of inappropriate antidiuretic hormone have been reported with tricyclic administration.

Other: Dizziness, tinnitus, weight gain, sweating, chills, fatigue, weakness, flushing, jaundice, alopecia, and headache have been occasionally observed as adverse effects.

Withdrawal Symptoms: The possibility of development of withdrawal symptoms upon abrupt cessation of treatment after prolonged SINEQUAN (doxepin HCl) administration should be borne in mind. These are not indicative of addiction and gradual withdrawal of medication should not cause these symptoms.

Dosage and Administration. For most patients with illness of mild to moderate severity, a starting daily dose of 75 mg is recommended. Dosage may subsequently be increased or decreased at appropriate intervals and according to individual response. The usual optimum dose range is 75 mg/day to 150 mg/day.

In more severely ill patients higher doses may be required with subsequent gradual increase to 300 mg/day if necessary. Additional therapeutic effect is rarely to be obtained by exceeding a dose of 300 mg/day.

In patients with very mild symptomatology or emotional symptoms accompanying organic disease, lower doses may suffice. Some of these patients have been controlled on doses as low as 25-50 mg/day.

The total daily dosage of SINEQUAN may be given on a divided or once-a-day dosage schedule. If the once-a-day schedule is employed the maximum recommended dose is 150 mg/day. This dose may be given at bedtime. **The 150 mg capsule strength is intended for maintenance therapy only and is not recommended for initiation of treatment.**

Anti-anxiety effect is apparent before the antidepressant effect. Optimal antidepressant effect may not be evident for two to three weeks.

Overdosage.
A. Signs and Symptoms
1. Mild: Drowsiness, stupor, blurred vision, excessive dryness of mouth.
2. Severe: Respiratory depression, hypotension, coma, convulsions, cardiac arrhythmias and tachycardias.

Also: urinary retention (bladder atony), decreased gastrointestinal motility (paralytic ileus), hyperthermia (or hypothermia), hypertension, dilated pupils, hyperactive reflexes.

B. Management and Treatment
1. Mild: Observation and supportive therapy is all that is usually necessary.
2. Severe: Medical management of severe SINEQUAN overdosage consists of aggressive supportive therapy. If the patient is conscious, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, should be performed even though SINEQUAN is rapidly absorbed. The use of activated charcoal has been recommended, as has been continuous gastric lavage with saline for 24 hours or more. An adequate airway should be established in comatose patients and assisted ventilation used if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported. Arrhythmias should be treated with the appropriate antiarrhythmic agent. It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 mg to 3 mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, however, barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis generally are not of value in the management of overdosage due to high tissue and protein binding of SINEQUAN.

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BUT PSYCHIATRY WAS THE REAL WINNER.

The American Psychiatric Association has announced that Ira David Glick, M.D., John E. Gudeman, M.D., and Jeffrey A. Borenstein, M.D., are this year's recipients of the PIA Foundation Awards for Hospital Psychiatry Research.

Dr. Glick is currently Professor of Psychiatry at Cornell University Medical College and Associate Medical Director for inpatient services at the Payne Whitney Clinic of New York Hospital. A dedicated researcher for more than two decades, Dr. Glick is widely published on the treatment of schizophrenia, inpatient family intervention, and length of psychiatric hospitalization. He is a 1987 recipient of a Fulbright Research Grant.

Dr. Gudeman is currently Associate Professor of Psychiatry at Harvard Medical School and Director of the Massachusetts Mental Health Center. Widely recognized for his research on the care and treatment of severe mental illness, Dr. Gudeman developed the Day Hospital/Inn model of care, and has written extensively on this subject.

A resident in psychiatry at New York University Medical Center and a 1986 APA/Mead Johnson Fellow, Dr. Borenstein has demonstrated an outstanding academic career and a commitment to the healthcare problems of older Americans. He co-developed methods for assessing levels of impairment and emotional and behavioral changes among Alzheimer's patients.

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Warnings: The risk of developing potentially irreversible *tardive dyskinesia* is believed to increase as duration of treatment and total cumulative dose increase, although it is impossible to predict who will develop the syndrome. It can also develop, although much less commonly, after brief treatment with low doses. Incidence appears to be highest among the elderly, especially elderly women. Generally chronic treatment should be reserved for chronically ill patients whose disease is most likely to respond to neuroleptic drugs and for whom other effective, less harmful treatment is not available or appropriate. There is no known treatment for tardive dyskinesia although the syndrome may partially or completely remit upon withdrawal of neuroleptic treatment. If signs and symptoms of tardive dyskinesia appear, drug discontinuation should be considered. Administer cautiously to patients who have previously exhibited a hypersensitivity reaction (e.g., blood dyscrasias, jaundice) to phenothiazines. Phenothiazines are capable of potentiating central nervous system depressants (e.g., anesthetics, opiates, alcohol, etc.) as well as atropine and phosphorus insecticides; carefully consider benefit versus risk in less severe disorders. During pregnancy, administer only when the potential benefits exceed the possible risks to mother and fetus.

Precautions: There have been infrequent reports of leukopenia and/or agranulocytosis and convulsive seizures. In epileptic patients, anticonvulsant medication should also be maintained. Pigmentary retinopathy, observed primarily in patients receiving larger than recommended doses, is characterized by diminution of visual acuity, brownish coloring of vision, and impairment of night vision; the possibility of its occurrence may be reduced by remaining within recommended dosage limits. Administer cautiously to patients participating in activities requiring complete mental alertness (e.g., driving), and increase dosage gradually. Orthostatic hypotension is more common in females than in males. Do not use epinephrine in treating drug-induced hypotension since phenothiazines may induce a reversed epinephrine effect on occasion.

Neuroleptic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. Daily doses in excess of 300 mg should be used only in severe neuropsychiatric conditions.

Information for Patients: It is suggested that all patients who are candidates for chronic treatment be advised of the risk of tardive dyskinesia.

Adverse Reactions: *Central Nervous System*—Drowsiness, especially with large doses, early in treatment; infrequently, pseudoparkinsonism and other extrapyramidal symptoms; rarely, nocturnal confusion, hyperactivity, lethargy, psychotic reactions, restlessness, and headache. *Autonomic Nervous System*—Dryness of mouth, blurred vision, constipation, nausea, vomiting, diarrhea, nasal stuffiness, and pallor. *Endocrine System*—Galactorrhea, breast engorgement, amenorrhea, inhibition of ejaculation, and peripheral edema. *Skin*—Dermatitis and skin eruptions of the urticarial type, photosensitivity. *Cardiovascular System*—ECG changes (see *Cardiovascular Effects* below). *Other*—Rare cases described as parotid swelling.

It should be noted that efficacy, indications and untoward effects have varied with the different phenothiazines. It has been reported that old age lowers the tolerance for phenothiazines; the most common neurological side effects are parkinsonism and akathisia, and the risk of agranulocytosis and leukopenia increases. The following reactions have occurred with phenothiazines and should be considered whenever one of these drugs is used:

Autonomic Reactions—Miosis, obstipation, anorexia, paralytic ileus. *Cutaneous Reactions*—Erythema, exfoliative dermatitis, contact dermatitis. *Blood Dyscrasias*—Agranulocytosis, leukopenia, eosinophilia, thrombocytopenia, anemia, aplastic anemia, pancytopenia. *Allergic Reactions*—Fever, laryngeal edema, angioneurotic edema, asthma. *Hepatotoxicity*—Jaundice, biliary stasis. *Cardiovascular Effects*—Changes in the terminal portion of electrocardiogram including prolongation of Q-T interval, lowering and inversion of T-wave, and appearance of a wave tentatively identified as a bifid T or a U wave have been observed with phenothiazines, including Mellaril (thioridazine); these appear to be reversible and due to altered repolarization, not myocardial damage. While there is no evidence of a causal relationship between these changes and significant disturbance of cardiac rhythm, several sudden and unexpected deaths apparently due to cardiac arrest have occurred in patients showing characteristic electrocardiographic changes while taking the drug. While proposed, periodic electrocardiograms are not regarded as predictive. Hypotension, rarely resulting in cardiac arrest. *Extrapyramidal Symptoms*—Akathisia, agitation, motor restlessness, dystonic reactions, trismus, torticollis, opisthotonus, oculogyric crises, tremor, muscular rigidity, and akinesia. *Tardive Dyskinesia*—Characterized by involuntary choreoathetoid movements variously involving the tongue, face, mouth, lips or jaw (e.g., protrusion of the tongue, puffing of the cheeks, puckering of the mouth, chewing movements), trunk and extremities—may be recognized during treatment upon dosage reduction or withdrawal of treatment. Movements may decrease or disappear if further treatment is withheld, although this reversibility is more likely after short-term rather than long-term treatment. Since neuroleptics may mask the signs of tardive dyskinesia, reducing dosage periodically increases the likelihood of detecting the syndrome at the earliest possible time. *Endocrine Disturbances*—Menstrual irregularities, altered libido, gynecomastia, lactation, weight gain, edema, false positive pregnancy tests. *Urinary Disturbances*—Retention, incontinence. *Others*—Hyperpyrexia; behavioral effects suggestive of a paradoxical reaction, including excitement, bizarre dreams, aggravation of psychoses, and toxic confusional states; following long-term treatment, a peculiar skin-eye syndrome marked by progressive pigmentation of skin or conjunctiva and/or accompanied by discoloration of exposed sclera and cornea; stellate or irregular opacities of anterior lens and cornea; systemic lupus erythematosus-like syndrome.

Dosage: Dosage must be individualized according to the degree of mental and emotional disturbance, and the smallest effective dosage should be determined for each patient. [MEL-Z37—5/1/85]

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MEL-1185-29

THE AMERICAN JOURNAL OF PSYCHIATRY

Psychological and Interpersonal Issues in Space

Nick Kanas, M.D.

As future manned space missions become longer, and as crews become more heterogeneous, psychological and interpersonal factors will take on increasing importance in assuring mission success. On the basis of a review of more than 60 American and Soviet space simulation studies on Earth, along with reports from U.S. and Soviet space missions, the author identifies nine psychological and seven interpersonal issues, which are discussed along with pertinent research findings and examples from manned spaceflights. He concludes that more psychological and interpersonal research should be done under actual spaceflight conditions and offers suggestions.

(Am J Psychiatry 1987; 144:703–709)

The space shuttle has expanded man's capabilities in space, and plans for a space station will accelerate this involvement in the future. With more ambitious mission goals, longer flight durations, and increased heterogeneity of crew members, psychosocial factors will take on added importance in relation to mission success. Such factors have not been clearly delineated and understood. In this paper I attempt to isolate important psychological and interpersonal issues from the literature, with particular reference to long-duration manned space missions, such as a space station.

Stressors existing in space environments include weightlessness, danger, confinement, periods of extreme activity alternating with monotony, separation from family and friends, and interpersonal tensions among crew members. Although not all of these stressors exist in the Earth-bound situations that have been viewed as space simulations, this literature is revealing and contains a fair amount of empirical work (more than 60 studies). Similar psychosocial research has not been done in space. The reports from manned space missions generally are anecdotal and consist of National Aeronautics and Space Administration (NASA) and Soviet space documents, newspaper articles and press releases, and publications of astronaut and cosmonaut diaries and biographies. The scientific merit of these reports may be open to question because of potential bias and subjectivity. Nevertheless, they contain useful insights and present issues that are remarkably consistent with findings from the Earth-bound studies. For all of these reasons, both simulation studies and space reports were used as resource materials for this paper. The exception was material involving single individuals in isolation, since future space missions will include more than one person.

Although descriptions of specific missions appear elsewhere (1–6), a summary of important American and Soviet activities is necessary for orientation. American studies and reports came from polar expeditions, submarines, submersible and land-based simulators, and short-term and long-term space missions. Most of the Antarctic studies were done from 1955 to 1968, in conjunction with the International Geophysical Year or as a result of military interest in men living in polar regions. Many of these studies examined both naval and scientific personnel working under conditions of isolation, danger, and monotony for periods of up to 1 year. The submarine studies involved early missions of the *Nautilus, Triton, Seawolf,* and *Polaris* for periods of 1 to 3 months. These were all military missions, but psychological and interpersonal studies were performed on the crew members' mental health and interactions using questionnaires, diaries, and medical observations. The submersible simulators (*Sealab, Ben*

Presented in part at the 140th annual meeting of the American Psychiatric Association, Chicago, May 9–15, 1987, and at the 57th annual Scientific Meeting of the Aerospace Medical Association, Nashville, Tenn., April 20–24, 1986. Received Oct. 4, 1985; revised May 16, 1986; accepted July 16, 1986. From the Psychiatry Service, San Francisco Veterans Administration Medical Center; and the Department of Psychiatry, University of California, San Francisco. Address reprint requests to Dr. Kanas, Psychiatry Service (116A), VA Medical Center, 4150 Clement St., San Francisco, CA 94121.

Franklin, and *Tektite*) were all self-contained environments housing military and scientific personnel involved with undersea studies. Crews were subjected to psychological tests, sociometric and mood questionnaires, and monitoring from the surface. The missions took place in the late 1960s and in 1970, lasted from 15 to 60 days, and included a number of diverse crews, one of which comprised five women *(Tektite).*

The land-based simulator studies took place in the 1960s and early 1970s, with the purpose of observing small groups of men interacting under conditions of isolation, confinement, and monotony for periods of up to 3 months. Crews were monitored from the outside and were evaluated via psychological and interpersonal tests, questionnaires, and diaries. Project ARGUS investigated the interactions of two- and three-man groups whose members were selected for being compatible and incompatible with one another. Some pairs were isolated for periods of 8–21 days, whereas other pairs performed the same tasks but were free to leave the isolation rooms when they were finished. Both experimental and control pairs were matched on personality dimensions. The School of Aerospace Medicine (SAM) studies involved the isolation of two-, three-, and four-man crews in a space cabin simulator for 2–8 weeks. The other land-based simulations (General Electric, Lockheed, Douglas, McDonnell Douglas) were all conducted in specially built capsules by companies active in the aerospace industry. The crews comprised four to six men who were all civilians. Reports from spaceflights included short-term missions such as *Gemini, Apollo,* and the space shuttle and relatively long-term flights of *Skylab* in 1973–1974 involving three-man crews living in space for up to 84 days.

Sources of Soviet studies and reports included hypodynamia (enforced bed rest), land-based simulators, and short-term and long-term space missions. Hypodynamia information came from two major studies involving groups of civilians confined to bed for periods of up to 2 months. These took place in 1968 and included control groups whose members engaged in various amounts of physical activity. The men were monitored and took various psychological tests. Land-based simulator studies were similar to those described in the American literature. One closed ecological system study took place from 1967 to 1968 and involved three civilians living together for 1 year under conditions of isolation and confinement. The short-term space reports all dealt with *Soyuz* flights, and the long-term space missions were from the *Salyut* space station, where crews were confined for periods of up to 237 days.

PSYCHOLOGICAL ISSUES

A number of important psychological issues can be abstracted from the above sources: sleep problems; time sense disturbances; demographic effects; career motivation; stages of reaction to isolation; transcendent experiences; postflight personality changes; psychosomatic symptoms; and anxious, depressive, and psychotic reactions. Sleep problems have been observed in space, including such features as insomnia, poor quality of sleep, fatigue, and alterations in sleep cycles. For example, during the *Gemini* 7 mission, one astronaut was connected to an EEG transmitter, and 55 hours of data were collected. He slept poorly during his first night in space, but during the second night his sleep cycle began returning to normal. Both he and his crewmate felt tired during the mission and averaged only 5.3 hours of sleep per night (7). Sleep problems like these have been partially alleviated in space by adjusting work/rest cycles and by lowering cabin noise and lighting. However, sleep difficulties continue to occur, even on long-duration missions (6, 8–9). They also have been reported on submarine and Antarctic missions, where sleep has been initially poor but has gradually returned to normal over time (1, 2). In one study of four men in the Antarctic (10), REM and stage 3 sleep decreased, stage 4 sleep disappeared, and the men suffered from a virulent form of insomnia called the polar "big eye." Fitful sleep and fatigue also have been reported in Soviet hypodynamia studies (11) and in the SAM two-man space cabin simulator (12).

Several American and Soviet space travelers have complained of not having enough time to perform scheduled activities in space (8, 13, 14). For example, on the third manned *Skylab* mission *(Skylab 4),* the crew members fell behind in their schedule and began making errors on several experiments. This led to a disagreement: the astronauts said they were being pushed too hard, whereas ground control believed they were not working up to their capability (13). It has been found that it takes longer to perform activities in space than on Earth. In one study involving selected tasks on the three *Skylab* missions, over half of the tasks required more time for completion the first time they were performed in space than during preflight simulation (15, 16). Part of this apparent operator overload has been attributed to a distortion in time sense called time compression. According to one ad hoc working group, time compression "probably contains elements of excessive mental workload, information overload, and cognitive processing involving inferences, judgement, and decision-making, for which the data bases are insufficient" (5, p. 20). Disturbances in time sense also have been noted on submarine missions, where they have been related to morale and activity level (17), and in Soviet hypodynamia studies, where subjects have been observed to give premature reactions on time-interval tests (2). These time sense disturbances need to be further studied in space.

Demographic effects that might have some importance for future space missions have been observed during nonspace activities. In the *Sealab* program (18), aquanauts who came from smaller towns adjusted better than those who came from larger cities. It also was found that later-born divers showed less fear and

better performance than firstborn and only children. During the *Tektite* missions (19, 20), aquanauts from smaller towns showed higher performance, like in the *Sealab* program. Although later-born individuals seemed to be technically better divers, firstborn aquanauts were more comfortable in social situations and performed better overall. This latter difference from the *Sealab* findings was attributed to the lower stress conditions of the *Tektite* missions (e.g., roomier habitat located in shallower water) and to the notion that firstborns outperform later-borns when stress levels are low to moderate. Although many of the astronauts who have successfully flown have been firstborn children, the effects of demographic factors on performance in space have not been studied extensively.

The importance of career motivation was observed in a study of mental health problems in the Antarctic from 1964 to 1966. It was found that naval personnel showed more symptomatic distress than civilian scientists over the long winter months (21). For the navy men, insomnia increased 28%, hostility 39%, and depression 15%. The corresponding figures for the scientists were 4% for insomnia and 21% for hostility; depression actually decreased 2% (2). The explanation for these findings was that the scientists were motivated to perform work-related activities (e.g., experiments, scientific reports), whereas the navy men had little to do during the wintering-over period. During the *Tektite* missions (19, 20), teams led by a scientist-aquanaut performed more marine science than teams led by an engineer. This was attributed to the fact that the scientist as leader was more likely to facilitate performance of the primary mission task (e.g., scientific research) than the engineer. Findings such as these have relevance for future long-duration space missions, where scientists and pilot astronauts will work together under conditions that will be monotonous at times.

On the basis of his review of Antarctic and submarine missions, Rohrer (22) described three stages of reaction to conditions of isolation and confinement. The first stage was a period of heightened anxiety occurring during the first few days of the mission. The degree of anxiety was related to perceived danger, and it was during this phase that psychotic episodes were most likely to occur. The second stage was a period of gradually increasing boredom and depression. This phase occupied the greatest block of time and occurred as the men settled down and began routine duties. The final stage was a period of anticipation occurring near the end of the mission. During this time, adolescent and immature behavior, hypomanic affect, and increased aggression and hostility were most likely to become apparent. Elements of these three stages have been observed in several simulators (1, 2) and on *Salyut* missions (6, 8). For example, 3 days into the 211-day *Salyut 7* mission in 1982, one cosmonaut complained of a tension headache and wrote in his diary: "In the morning, I feel somewhat uneasy; after breakfast, a bit better. Work is a good distraction when it goes well" (8, p. 24). Nearly 4 months later, he wrote: "I begin having trouble falling asleep. I'm lying here like a teenage girl, thinking of different things and reminiscing about home. I fall asleep around 2 a.m. Before going to sleep, I like reading the newspaper, which I have read ten times before" (8, p. 28). Finally, the day before returning to Earth, he wrote: "Our mood is strange and anxious. How is everything down there? We're no longer used to it! We've learned to adapt to living on a small island in space, and now we have to face the real world again. It's an uneasy feeling" (8, p. 28).

Several astronauts and cosmonauts have described having transcendent experiences in space (16, 23). These have included a sense of awe and humility at the beauty of the Earth and the vastness of the cosmos (6, 8, 9, 23), a new understanding of life and the nature of God (9, 13, 23), and experiences bordering on derealization and hallucination (8, 16). For example, one *Apollo 15* astronaut stated "I felt the power of God as I'd never felt it before. My faith in God was freshened, and made more real. I consider that it's God's plan to come back and tell people what a beautiful thing we have here on Earth, to take care of it, and to try to live in brotherhood, the way Jesus Christ would want us to" (23, p. 13). Some of these experiences are reminiscent of the "break-off" phenomenon, which is a feeling of unreality and separation from Earth sometimes experienced by jet pilots flying under monotonous conditions (24); this phenomenon has been related to preexisting emotional and personality problems (25). Transcendent experiences in space need to be studied more fully since they may interfere with judgment. For example, during a 96-day *Salyut 6* mission in 1977–1978, one cosmonaut became so enraptured with his view from an open air lock that he made an impulsive, unauthorized extravehicular excursion and forgot to attach his safety line; fortunately, his fellow cosmonaut grabbed the line and pulled him to safety (6). Similarly, an astronaut caused a problem with the control system of *Skylab* when he became preoccupied with his view of the Earth and left his work station (9).

Personality changes have been observed in several astronauts and cosmonauts following flights into space. These usually involve a change in outlook, such as increased religiousness or sensitivity to human needs. One *Skylab* astronaut described this experience as follows: "I now have a new orientation . . . of almost a spiritual nature. My attitude toward life and toward my family is going to change. When I see people, I try to see them as operating human beings and try to fit myself into a human situation instead of trying to operate like a machine" (13, p. 146). Several astronauts have formed or joined spiritual or religious groups after returning to Earth (23). Difficulties adjusting to postflight life have been described as well, as in the case of one *Apollo 11* astronaut who experienced depression and marital problems after his return to Earth that necessitated psychiatric intervention (26). Psychological changes also have been described fol-

lowing space simulations. In a 1-year follow-up of the four crew members involved with the 90-day McDonnell Douglas simulator study in 1970, two were noted to be less anxious during subsequent Rorschach testing, while one was viewed as more anxious and suspicious (27). It is difficult to separate how much of this change was due to the confinement experience and how much was due to postmission factors in each man's life.

Psychosomatic symptoms have been described in space and have included headaches, gastrointestinal complaints, and fear of having physical problems. During the 175-day *Salyut 6* mission in 1979, a cosmonaut was quoted in his diary as follows: "In the actual flight, I was afraid most of all of an appendicitis attack. I still had my appendix. Also, I was afraid of getting a toothache. Once in flight I dreamed I had a toothache. I awoke almost instantly, feeling, yes, my tooth really did hurt. But by morning the pain was gone" (8, p. 30). Psychosomatic symptoms also have been reported during Antarctic expeditions, submarine missions, and land-based simulations (1, 2). For example, during the 83-day cruise of the *Triton* submarine, 25% of the men reported headaches during an average day (28), and several men were treated for headaches and somatic concerns during two *Polaris* cruises (29).

Although fear of dangerous situations and feelings of homesickness have been described by astronauts and cosmonauts (6, 8, 9), anxious, depressive, and psychotic reactions have not been reported in the American and Soviet space literature. One possible grief reaction may have been averted during the 96-day *Salyut 6* mission when it was decided to delay telling a cosmonaut about the recent death of his father until the mission was completed (6). However, psychiatric problems have occurred in polar, submarine, and hypodynamia studies (1, 2). In the Antarctic mental health study mentioned earlier (21), the number of anxious and depressive episodes increased between the beginning and end of the isolative winter months. In another Antarctic study (2), the incidence of a number of psychological symptoms (tension, irritability, suspiciousness, uncooperative behavior) increased over the course of the 1-year tour of duty. For example, three episodes of tension were reported in the first 4 months, eight in the next 4, and 19 in the last 4. In one submarine study (29), the incidence of anxious, depressive, and psychotic reactions was 5%. Although least frequent, psychosis may be disruptive on such missions, despite the fact that active psychotropic and psychotherapeutic interventions have prevented such episodes from interfering with mission success (30). How such occurrences will be handled in space remains to be seen.

INTERPERSONAL ISSUES

Important interpersonal issues include interpersonal tensions, problems resulting from crew heterogeneity, anger displaced to outside personnel, need for dominance, decreased cohesiveness over time, task-neutral interactions, and types of leadership. Interpersonal tensions have occurred in space but have not progressed to the point of interfering with mission goals (7, 8, 9, 31, 32). One cosmonaut has been quoted as saying that "joint existence cannot be serene. We had disagreements in flight. . . . The disagreement did not reach a scandal, inasmuch as there was no 'platform,' it was simply fatigue, and frequently simple inattention which would cause the argument" (32, p. 149). Antagonisms occurred during several SAM simulations, and arguments and fighting have been reported in the Antarctic, in submarines, and during Project ARGUS (1, 2). An interesting form of tension release called "pinging" has been noted on submarines, whereby one sailor teases another about some tender subject and wins the game if he can elicit an angry reaction (33). During the 30-day Douglas and 60-day McDonnell Douglas simulation studies (34, 35), interpersonal tensions were observed to be minimal. In part, this was attributed to the fact that subjects in both studies received 12–24 hours of sensitivity training before confinement which was designed to improve social awareness and behavioral flexibility. No such training took place prior to the 90-day McDonnell Douglas simulation study (36), and the interpersonal relations of the subjects during the confinement were observed to become increasingly tense, impersonal, and noninteractive. The air was cleared after a "bull session" took place between the subjects and the study's behavioral director. The effect of sensitivity training on space crews has not been evaluated, but this simulation experience supports the notion that such training might be useful in decreasing interpersonal tensions in space.

One potential source of tension in future long-term space missions relates to crew heterogeneity. How will career pilot astronauts interact with individuals going into space for a specific purpose involving scientific, political, economic, or other goals? How will men and women relate? Despite publicized equality, male cosmonauts have evidenced sexual stereotyping toward their female counterparts (6, 8). For example, cosmonaut chief Shatalov has been quoted as saying that spaceflight is too demanding for women (6), and a *Salyut 7* cosmonaut on a 211-day mission wrote of his female counterpart: "We waited for her to make her appearance. And just like a woman, she kept primping" (8). How will people of different backgrounds and nationalities interact? Cultural differences may be subtle but are important. For example, it has been noted that people from Arab countries tend to stand close together during conversation, whereas Americans reserve physical closeness for intimacy or aggression (8). Would such closeness be misinterpreted in space? Language, cultural, and political differences have created some disruptions on Soviet international spaceflights (6, 8, 31, 32). A Czech cosmonaut sardonically joked that his hands had turned red during his

visit to *Salyut 6* since "whenever I reached for a switch or a dial or something, the Russians shouted, 'Don't touch that!' and slapped my hands" (6, p. 184). Such difficulties have not been reported on American space shuttle flights, but it is possible that tensions relating to crew heterogeneity will become problems under the conditions of monotony and long-term confinement on future space missions.

A phenomenon commonly observed during spaceflights and simulations is a tendency for confined individuals to get angry at the outside personnel (1, 2, 8, 13, 14). During the first *Spacelab* flight aboard the space shuttle in December 1983, a scientist astronaut repeatedly expressed anger at ground control for interrupting and overworking the crew (14). A similar episode on *Skylab 4* led to a work slowdown, and the block was resolved only after an open, frank bull session, when work schedules were adjusted and crew members were given more time to relax (13, 37). In simulators, anger directed to the outside has tended to occur in studies where overt anger was not observed between the confined subjects, leading to speculation that this phenomenon is a displacement of interpersonal tensions to safer, more remote individuals. For example, anger directed to the outside monitors was observed during the interpersonally calm 30-day Douglas and 60-day McDonnell Douglas studies (34, 35), whereas such displacement was not observed during the strife-ridden 90-day McDonnell Douglas study (36). This phenomenon needs to be studied during actual space missions in order to minimize its potential for creating serious divisions between space crews and ground control.

During Project ARGUS, it was found that pairs of men who were isolated and who were both high in need for dominance on the Edwards Personal Preference Scale interacted poorly and showed territoriality by physically withdrawing from each other (38). In contrast, the matched pairs in the nonisolated condition experienced no arguments. Similar problems occurred between immature, aggressive men who were confined in the SAM four-man simulator (39). These findings support the notion that the stresses of isolation and confinement may be affected by the relations between personality types, especially in the area of need for dominance. Similar observations have not been reported from space, perhaps because astronauts and cosmonauts have been selected carefully through use of rigorous psychological testing, clinical interviewing, and performance criteria (40). However, selection will be less rigorous in the future, particularly for crew members who are not career NASA employees. Rapid means of screening out candidates who are unsuitable and screening in crews that comprise compatible individuals need to be developed, and both intrapsychic and interpersonal considerations should be addressed.

Records from long-term *Salyut* flights, Antarctic and submarine missions, and simulators have described decreased cohesiveness among crew members over time (1, 2, 6, 8). For example, 2 months into his 211-day mission, one *Salyut 7* cosmonaut wrote in his diary: "The hardest thing during a flight is keeping good relations going with the ground and among the crew. With growing fatigue, there is a danger of serious lapses. There are tense moments, but they cannot be allowed to explode. Otherwise a crack, once it appears, can widen . . . . The flight becomes increasingly difficult. Looking out the window is calming" (8, p. 28). The *Skylab* astronauts also received much satisfaction from looking out the window and having time to themselves (37). One *Skylab 4* astronaut wrote that "a lack of privacy adds to interpersonal tensions" (41, p. 38), and much care was given on *Skylab* to establishing separate compartments with fabric doors into which each astronaut could go and be alone to sleep, read, or introspect. This need for privacy is reminiscent of the increased territoriality and withdrawal observed over time during Project ARGUS and other simulation studies (1, 2). Two additional manifestations of decreased cohesiveness are subgrouping and scapegoating. Subgroups were common in the Antarctic and on submarines and seemed to form along work-related lines—for example, scientists, cooks, and enginemen (1, 2). Scapegoating also occurred, and a particularly virulent form was the "long eye" phenomenon described by Rohrer (42). This was an extreme form of the silent treatment given to a deviant crew member which often resulted in sleeplessness, crying outbursts, hallucinations, despondency, and aimless behavior. As soon as the person was permitted to interact with the group, these symptoms disappeared. Since performance is dependent on crew member cohesiveness, mission goals may be adversely affected by such behavior in future manned spaceflights.

The piloting and scientific demands of space missions require that facts and instructions be communicated among crew members and between the crew and ground control. Consequently, many of the comments that are made involve information transfer. This also was observed in a SAM simulator study using the Bales Interaction Process Analysis, which is a method of scoring interactions between individuals into one of 12 categories (43). Flinn and his colleagues found that there was a significantly higher proportion of interactions involving the giving and receiving of information and opinion in the SAM simulator than in a composite of 21 other studies of small groups (43). Conversely, there were fewer social-emotional interactions, particularly involving negative emotions. What is not clear is whether task-neutral interactions were used to avoid more personal contact. For example, during his 175-day mission, a *Salyut 6* cosmonaut wrote in his diary: "In space we discovered that neither of us is garrulous. We rarely talked about things other than work. Sometimes after communications sessions with our families we gave in and talked about things we remembered" (8, p. 30). It would be interesting to study the interactions of astronauts and cosmonauts in space during

free time and compare these interactions with those during work periods.

On short-term space missions and submarines, the leadership structure is clearly established. This comes from the military tradition, where lines of authority are delineated in terms of task responsibility. In sociometric studies on board the *Sealab* submersible, it was found that the most desired leaders were rated as being more task-oriented and aloof as compared with leaders who were more social and interactive with the crew members (18). In contrast, during longer Antarctic missions, status leveling occurred over time, with the most valued leaders being characterized as having a democratic style and showing concern for the well-being and emotional state of their men (44, 45). On the 96-day *Salyut 6* mission, the commander was a young rookie and his partner was an older veteran whose engineering skills were needed to repair the space station. To avoid competition, the men decided to share decision making through mutual discussion, with apparent success (6). Finally, as mentioned previously, teams led by scientists were more productive than teams led by engineers during the science-oriented *Tektite* missions (19, 20). It is difficult to predict what type of leadership will be preferred on future long-term space missions, especially where mission goals are complicated and where monotony enters in as an important stressor.

RESEARCH IMPLICATIONS

Despite the value of simulation studies and reports from space, psychosocial research needs to be done under actual spaceflight conditions. Several research areas are suggested. First, rapid screening methods that not only assess motivation and covert psychopathology but also predict which individuals will form compatible space crews need to be developed and studied. For example, using interviewing and testing techniques, investigators were able to predict crew incompatibilities on the *Ben Franklin* submersible mission (46), and interpersonally oriented paper and pencil tests such as the Fundamental Interpersonal Relations Orientations—Behavior have shown promise in crew selection in a number of simulators (34, 38, 46). Second, crew members should be briefed on important psychological and interpersonal issues that might affect mission success. This would allow them to become aware of danger signs and useful coping strategies. Sensitivity training and bull sessions have been used successfully in simulators and on *Skylab 4* (13, 34–36), and group techniques found useful in helping professionals cope with job-related stress might be applied as well (47–49). The effectiveness of such experiences could be tested by measuring mission performance of crews receiving and not receiving such training. Third, crew member interactions in space need to be studied at different stages in the mission, with particular reference to types of interactions (e.g., task-neutral versus social-emotional), signs of developing interpersonal tensions, and formal versus informal leadership structure. Sociometric techniques and process measures such as the Bales Interaction Process Analysis lend themselves to such study in space (50) and have been used successfully in the Antarctic and in space simulators (18, 19, 35, 43, 51). Finally, strategies should be developed and tested that would identify and deal with psychiatric emergencies in space, such as acute psychotic or suicidal reactions. For example, the Soviets have reported success in using the analysis of objective characteristics of speech, as measured through recordings of space transmissions, as an indicator of cosmonaut stress and emotional state (52, 53). In contrast, a similar analysis of fundamental and formant frequencies of selected *Skylab* communications was judged to be insufficiently predictive of crew member stress to warrant further use (54). Another approach would be to have at least one crew member on future space missions trained in the use of psychotherapeutic and psychopharmacological interventions. When a psychiatrist in space is not feasible, psychiatric consultation should be freely available from Earth via audiovisual transmissions. Such communication links have been used during *Salyut* missions to help ground controllers capture subtle nuances in the cosmonauts' mood (6, 55).

Research involving the above areas could be accomplished in conjunction with space shuttle flights, thus providing important data that could be used in planning longer-term missions, such as a space station or a trip to Mars. This research needs to be conducted unobtrusively, and crew member confidentiality and privacy must be protected as much as possible. The information gained would help to minimize psychological and interpersonal risks, thus improving the chances of success in future manned space missions.

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Childhood Cruelty to Animals and Later Aggression Against People: A Review

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The existing literature on the relationship between childhood cruelty to animals and later violence against people appears to be inconsistent. The authors review the controlled studies that did not support this relationship and those that did and identify several methodological factors that may have contributed to the contradictory findings. Studies using direct interviews to examine subjects with multiple acts of violence point to an association between a pattern of childhood animal cruelty and later serious, recurrent aggression against people. Identification of such a relationship could improve understanding of impulsive violence and facilitate early intervention and prevention.

(Am J Psychiatry 1987; 144:710–717)

In 1806 Phillipe Pinel advanced the diagnostic concept of "mania without delirium," often cited as a nosological forerunner of antisocial personality disorder. Individuals with this disorder were not lacking in understanding, but they "were under the domination of instinctive and abstract fury, as if the active facilities alone sustained the injury" (1). The first of Pinel's two examples of this disorder involved a man who aggressed against people in various ways and eventually killed a person. "If a dog, a horse, or any other animal offended, he instantly put it to death" (1).

Since Pinel's observation, a number of case examples of dangerously aggressive men who had been cruel to animals during childhood have been entered in the literature. Some of the most notorious mass and multiple murderers, historically and in recent years, reportedly had behavioral patterns of excessive cruelty to animals in childhood (2–4). At least in these few but extremely violent individuals, animal cruelty was one of several symptomatic behaviors indicative of poorly controlled aggression.

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Nevertheless, an association between cruelty to animals and violence against people is not uniformly accepted by psychiatrists for several reasons. There is concern about attaching undue importance to any single symptom. Empirical studies that have tested this hypothetical association appear to have resulted in contradictory findings. The data supporting this association are considered "soft" and of dubious reliability. The methods of sample selection limit the generalizability of the positive findings and conclusions. Therefore, the claims for the value of animal cruelty and other behaviors in predicting violence seem to have been overstated. And, if the predictive value is meager, any real association is interesting but useless.

In the present inquiry we will review controlled studies that pertain to a possible association between animal cruelty and violence against people. We will summarize the current state of scientific knowledge on this issue. Many of the studies cited here included animal cruelty as only one item of a more widely encompassing inquiry. Our focus precludes analysis of methods and findings that do not directly relate to animal cruelty in particular.

Before reviewing studies that pertain to animal cruelty, we should address the concern about focusing too much attention on a single symptom. Certainly for purposes of diagnosis, one symptom should not be elevated to the exclusion of others that are also clinically significant. This is especially true for disorders manifested by multiple aggressive and antisocial behaviors. In terms of *DSM-III*, this criticism does not apply to animal cruelty because this behavior is not mentioned as symptomatic of any disorder.

The question addressed in this review is whether the scientific literature supports an association between a pattern of repeated, substantial cruelty to animals in childhood and later violence against people that is serious and recurrent. First, controlled studies that tested this association but did not find it to be significant will be reviewed. Second, we will examine controlled studies that did find a statistically significant association. Unfortunately, the constraints of space do not allow inclusion of a number of uncontrolled studies that pertain to this issue (5–13). This review will not include reports of single cases involving animal cruelty or studies of aggressive behaviors that are not clearly injurious or dangerous.

TABLE 1. Studies That Found No Clear Association Between Childhood Cruelty to Animals and Later Violence Against People

Author	Setting	Subjects			Method of Data Collection	Childhood Cruelty to Animals (%)
		Type	N	Sex		
Macdonald (14)	VA hospital psychiatric unit	Nonaggressive patients	20	—	Interview	—
		Patients who threatened to kill	20	—	Interview	—
		Killers	20	—	Interview	—
Climent et al. (15)	Hospital emergency room	Violent patients	40	M/F	Interview	—
		Nonviolent patients	40	M/F	Interview	—
Climent et al. (16)	State prison	Prisoners	95	F	Interview	—
Sendi and Blomgren (17)	Children's psychiatric service	Homicidal adolescents	10	M	Chart review	20
		Adolescents who threatened or attempted homicide	10	M	Chart review	30
		Control patients	10	M	Chart review	30
		Nonviolent patients	40	M/F	Interview	—
Rada (18)	Prison	Rapists	20	M	Interview	35
		Nonviolent child molesters	20	M	Interview	30
Felthous and Bernard (19)	Private psychiatric hospital	Patients	133	M/F	Chart review	—
Lewis et al. (20)	Children's inpatient psychiatric service	Homicidal patients	21	M/F	Chart review	14
		Nonhomicidal patients	30	M/F	Chart review	3
Shanok et al. (21)	Children's psychiatric service	Delinquent adolescents	29	M	Chart review	0.0
		Nondelinquent adolescents	25	M	Chart review	8.3
Langevin et al. (22)	Forensic inservice	Killers	109	M/F	Chart review	8
		Nonviolent offenders	38	M/F	Chart review	0
	Community	Normal control subjects	54	M/F	Chart review	—
Prentky and Carter (23)	Prison hospital	Sex offenders	206	M	Chart review	7.8

STUDIES THAT FOUND NO CLEAR ASSOCIATION

Controlled studies that found no clear association between cruelty to animals and personal violence are summarized in table 1. In 1968 Macdonald (14) reported a controlled study that was designed to test nine variables, including cruelty to animals, thought to predict homicide. Three groups of patients in a VA hospital psychiatric unit were interviewed: 20 homicide offenders, 20 inpatients who had threatened to kill, and 20 inpatients with no history of homicide or homicidal threats. Macdonald conducted a semistructured interview with each subject. Animal cruelty was defined as the deliberate infliction of injury or death on "animals or birds" in a sadistic manner.

None of the variables was significantly associated with any of the three groups. However, in discussing the homicide offenders, Macdonald commented, "The incidence of only one factor, cruelty to animals, exceeded the higher incidence of the various factors in the homicide-threat and matched homicide-offender groups. The higher incidence of cruelty to animals might be expected in a group which included more sadistic offenders" (14, p. 62).

In a well-controlled study of 40 violent and 40 nonviolent patients in a hospital emergency room, Climent et al. (15) found no discernible difference in childhood cruelty to animals. The violent subjects had come to the emergency room with a chief complaint of violence. Their acts were typically repetitive. A trained research assistant, who was blind to the objectives and hypotheses of the investigation, obtained data by administering a questionnaire. Fourteen of the items dealt with "neurotic childhood traits." Cruelty to animals was one of several items for which no difference was found between the two groups. Stubbornness, temper tantrums, and emotional deprivation were associated with the violent sample.

Climent et al. (16) reported in 1973 a multidisciplinary study of 95 female prisoners. The authors did not define violence, and the nature of aggression studied can be inferred only from the five variables used to distinguish violent from nonviolent inmates: 1) a particular MMPI profile, 2) reports and ratings by correctional officers, 3) commission of a violent crime, determined by prison administrators who reviewed the inmates' criminal histories, 4) length of current sentence beyond the mean sentence of 5.2 years, and 5) an elevated score on a self-evaluation questionnaire about various violent behaviors.

The data were gathered by several methods, but it appears that the historical items were tested by means of a 189-item standardized questionnaire. An item that was associated with all five measures of violence was considered to be associated with violence.

Childhood cruelty to animals was one of several items that Climent et al. identified as reaching "near-significance" in association with violence. From this study of incarcerated women, it cannot be concluded whether or not cruelty to animals is associated with recurrent, diffuse physical aggression directed against people.

Sendi and Blomgren (17) reported a comparative study of 10 adolescent boys who had committed homicide, 10 who had attempted or threatened homicide, and 10 psychiatric control subjects. The subjects in all three groups had been admitted to a child psychiatric inpatient service. An evaluative form was prepared for systematic data collection. The case his-

tories were reviewed, and the boys' behavior was observed for 1 week by two independent raters.

The triadic behaviors of persistent enuresis, fire setting, and animal cruelty were evenly distributed among the three groups. None of the patients had the complete triad. Most of the adolescent murderers had a diagnosis of schizophrenia, whereas most who threatened or attempted homicide had a diagnosis of organic brain syndrome. Exposure to parental brutality and domestic violence was associated with the homicide group.

Rada (18) briefly reported the results of a comparative retrospective study of 20 rapists and 20 nonviolent child molesters. Evidently, the subjects in both groups were interviewed directly. Childhood enuresis was reported by 45% of the rapists, cruelty to animals by 35%, and fire setting by 30%. The comparable figures for the child molesters were 45%, 30%, and 15%, respectively. Ten percent of the rapists had a positive triad, as did 5% of the child molesters. Rada concluded that the predictive value of the triadic behaviors was undetermined.

In 1979 Bernard and one of us (A.R.F.) (19) reported a retrospective study of 133 male and female patients in a private psychiatric hospital. Charts of male and female patients between 15 and 30 years of age were selected in order of hospital discharge. Information was collected by means of a data retrieval outline and chart review. Most patients with a single triadic behavior lacked a history of interpersonal violence. Those with two or three triadic behaviors also had a recorded history of at least two of the following behaviors: homicidal threats, carrying a deadly weapon, and physical assaults. The numbers were too small for statistical analysis. One useful result of this study was its demonstration that chart review is a weak means of systematically obtaining comprehensive and reliable historical data.

In 1983 Lewis et al. (20) reported a study of 55 children, 3 to 12 years of age, who were admitted to a psychiatric inpatient service. Only one episode of "homicidal behavior" was required to classify the child as homicidal. The behavior was assessed by four independent raters, each of whom determined whether the act would have resulted in death or serious injury had it been performed by an adult. Threatening with a lethal weapon was considered equivalent to a homicidal act. For the purposes of the study, 21 children were classified as homicidally aggressive, and 30 were considered not homicidally aggressive. The data were obtained from the patients' hospital records. Lewis et al. found, "The proportions of homicidally aggressive and nonhomicidal children with histories of cruelty to animals (14% and 3%) . . . [were] not significantly different" (20).

They conceded, "Data are not uniform or complete because they are not collected primarily for research purposes. On the other hand, data obtained from retrospective chart reviews of symptoms and behaviors are unbiased by the possible prejudices of the investigators." Since the aggressive sample was selected on the basis of a single episode of homicidal behavior, the study did not discriminate recurrently aggressive children.

Shanok et al. (21) reported a study of 29 delinquent and 25 nondelinquent adolescent boys admitted to an inpatient psychiatric service. Data were gathered from hospital and probation department records. A symptom was considered to be present if a clinician had noted its occurrence and given an example in the chart. Significantly more delinquent than nondelinquent boys had acted violently in the past, and significantly more delinquent boys had been hospitalized before. But the triadic elements did not distinguish the two groups. Cruelty to animals was reported in the charts of only two nondelinquent boys; it was not recorded in any of the delinquent boys' charts.

In 1983 Langevin et al. (22) reported a study of 109 killers and 38 nonviolent offenders in a forensic inservice and 54 normal control subjects. The records of 50% of the offenders included a standardized Parent-Child Relations Questionnaire. Data were obtained from each chart by two raters and were checked for interrater reliability. The killers had disturbed parent-child interactions, but they did not differ from the nonviolent offenders in this regard. Compared to the killers, more of the nonviolent offenders ran away from home, more were adopted, but fewer stole in childhood. The triadic behaviors were not significantly associated with any of the three groups, but the only subjects with either two (N=6) or three (N=1) of the triadic behaviors belonged to the killer sample. Cruelty to animals was noted more often in the killers than in the nonviolent offenders (8% versus 0%).

As Langevin et al. pointed out, cruelty to animals and other childhood behaviors will not be registered if an initial evaluator, unconnected with the study, failed to inquire about this behavior or to record it in the patient's chart. For this reason, historical information gleaned from charts can be expected to yield lower frequencies than direct interviews with subjects. In comparing Langevin et al.'s results with those of other studies, one should also note that the index sample consisted of patients charged with a homicidal offense. Aggressive individuals were not defined as those with long-standing patterns of diffuse, impulsive personal violence.

Prentky and Carter (23) reported in 1984 a study of 206 male sexual offenders who were incarcerated for evaluation and treatment, having been adjudged to be "sexually dangerous." Data were obtained by systematic review of each inmate's chart. The charts were randomly assigned to three research assistants to review. The variables tested for association with the triadic behaviors fell into four groupings: family, childhood, juvenile, and criminal. The variables that most closely correspond to recurrent personal violence appear to be "total number of adult and juvenile serious sexual . . . crimes" and "degree of violence of the most violent offense."

TABLE 2. Controlled Studies That Found a Significant Association Between Childhood Cruelty to Animals and Later Violence Against People

Author	Setting	Subjects			Method of Data Collection	Childhood Cruelty to Animals (%)	Significance
		Type	N	Sex			
Hellman and Blackman (24)	Prison hospital	Violent prisoners	31	M	Interview	52	$\chi^2=16.63$, $p<.001$
		Nonviolent prisoners	53	M	Interview	17	
Felthous and Yudowitz (25)	State prison	Violent prisoners	11	F	Interview	36	$p<.02$ (chi-square analysis)
		Nonviolent prisoners	13	F	Interview	0	
Felthous (26)	Inpatient psychiatric service of military hospital	Violent patients	74	M	Interview	18	$p<.025$ (chi-square analysis)
		Nonviolent patients	75	M	Interview	5	
Kellert and Felthous (28, 29)	Federal prisons	Violent prisoners	32	M	Interview	25	$\chi^2=30.56$, df=9, $p<.005$
		Prisoners of intermediate violence	18	M	Interview	0	
		Nonviolent prisoners	52	M	Interview	6	
	Community	Nonprisoners	50	M	Interview	0	

To the extent that the variables were tested for an association with measures of aggression, the study was controlled, but all the subjects were adjudged to be "sexually dangerous"; no "sexually nondangerous" control subjects were studied for comparison.

Although cruelty to animals and arson were not defined, the study apparently identified a respectable number of subjects with a partial or complete triad (N=81). Compared with the subjects without any triadic elements (N=103), more of the triadic subjects came from abusive family backgrounds. In comparison with the subjects who had not been physically abused, over twice as many subjects who were physically abused in childhood also had histories of triadic behaviors. Compared with the subjects who had not been sexually abused, over four times as many subjects who had been sexually abused in childhood had triadic behaviors. Prentky and Carter concluded that triadic behaviors represent "primarily a maladaptive response to turmoil and abuse in the home prior to and during adolescence" (23). The study did not find a relationship between adult crime and the complete triad (N=4), a dyad (N=14), or a monad (N=63). Sixteen of the subjects (7.8%) had been cruel to animals.

Because the data were obtained from chart reviews, it is not clear that all subjects had been asked directly about cruelty to animals. And since the variables relating to aggression were convictions of violent crimes, the question of whether animal cruelty and other triadic behaviors are associated with recurrent personal violent acts, which do not invariably result in conviction, remained unanswered.

STUDIES THAT FOUND AN ASSOCIATION

Controlled studies that found an association between cruelty to animals and personal violence are summarized in table 2. The most frequently cited study and the first to lend statistical support to the impression that childhood triadic behaviors are associated with later aggression against people was reported by Hellman and Blackman in 1966 (24). The study involved interviews of 31 male prisoners charged with violent crimes and 53 male prisoners charged with nonaggressive crimes. Three-fourths of the aggressive men gave histories of triadic elements, whereas only 15 of the 53 nonviolent men had these childhood behaviors. Two-thirds of those revealing a positive triad belonged to the aggressive group. Animal cruelty was reported by 16 (52%) of the 31 aggressive prisoners and by nine (17%) of the 53 nonaggressive prisoners ($\chi^2=16.63$, $p<.001$).

The subjects were selected and assigned to the violent or nonviolent sample on the basis of a single charge; thus, this study did not differentiate recurrent from isolated aggressive acts. However, 75% of the violent subjects had a background of rapes, burglaries, and assaults before the index offense, so most may have been recurrently and diffusely aggressive, even though they were not selected on the basis of multiple acts of aggression. One must wonder whether the association would have been more specific had the investigators discriminated recurrent violence.

Hellman and Blackman noted that a social history was not always effective in obtaining a history of cruelty to animals. As in the case of fire setting, the relatives were not always aware of this behavior. Our experience also suggests that confirmation by relatives is often impossible.

In 1977 Yudowitz and one of us (A.R.F.) (25) reported a two-part study of female offenders that was designed to test variables thought to be associated with violence against people. One portion of the study compared 31 female offenders with 19 male offenders to determine whether historical items distinguished the women from the men. Data were obtained by administering a questionnaire and then an interview. The male sample had a higher prevalence of killing animals, but torturing animals, like enuresis and fire setting, was of nearly equal prevalence in the two samples. The numerical data did not differentiate animal killings that were deviant or gratuitous from socially acceptable killings.

In the second part of this study, assaultive and nonassaultive women were compared. An assaultive woman was defined as one convicted of a violent offense against a person (N=11), whereas a nonassaultive woman had no record of charges or convictions of a violent offense (N=13). Cruelty to animals was the only childhood behavior that differentiated the two groups with statistical significance (chi-square analysis, $p<.02$).

It should be noted that a conviction of a violent offense does not establish a pattern of recurrent aggression, and lack of a charge of a violent offense does not rule out a pattern of interpersonal violence.

One of us (A.R.F.) (26) reported in 1980 a study of 429 patients who were admitted to a Navy hospital, 346 men and 83 women. The subjects were not selected on the basis of aggressive behaviors or any other symptoms; they were patients successively admitted to the psychiatric service who were available and willing to participate. From the 346 men interviewed, 74 were identified as aggressive on the basis of 1) a history of assault serious enough to require the victim to obtain medical treatment or dental restoration or 2) either threatening serious harm against others or carrying a knife or gun for potential use against others. Most who manifested several types of aggressive behaviors also had histories of recurrent assaults. The nonaggressive male subjects (N=75) lacked a history of any of these behaviors since the age of 15. Historical variables thought to be associated with violence were tested via an interview schedule.

Killing dogs or cats and animal cruelty were significantly associated with the aggressive group (chi-square analysis, $p<.025$), but other childhood behaviors showed a stronger correlation: violent outbursts, fights, fights resulting in injury, school suspensions, school truancy, and frequent temper tantrums (in all cases, $p<.005$).

The latter behaviors correlated more strongly because they were reported by more of the aggressive subjects. However, these behaviors were not uncommonly reported by the nonaggressive subjects as well. The number of subjects who were pugnacious as young children but nonaggressive after 15 years of age was over half the number who were pugnacious as children and dangerously aggressive later on. In contrast, although childhood animal cruelty was reported by only 18% of the aggressive sample, the number of subjects with this behavior was several times higher among the aggressive subjects (N=13) than among the nonaggressive subjects (N=4).

The aggressive sample was also compared with a nonpsychiatric sample of men admitted to another service of the same hospital (N=26). The symptomatic items for which statistical significance was upheld in both comparisons included fights with or without injury, school truancy, school suspensions, frequent headaches, and killing dogs or cats (chi-square analysis, $p<.05$ in all cases).

From the 346 male psychiatric inpatients included in that study, those whose history of cruelty to animals consisted of repeatedly torturing and injuring dogs or cats (N=18), regardless of level of aggression, were singled out (27). This animal cruelty group was clearly skewed toward a higher level of aggression against people. Specifically, nine animal cruelty subjects belonged to the most aggressive level, whereas only one belong to the least aggressive level and the other eight were disturbed over intermediate levels of aggression. A control group was defined as subjects with the highest level of aggression toward people who denied a history of cruelty to animals in childhood (N=53).

The historical items reported by a majority of both samples included childhood fighting, temper tantrums, brutal punishments by a father figure, brutal punishments by a mother figure, violent outbursts, and school truancy. Setting uncontrolled fires was significantly associated with the animal cruelty group. Poor school work, setting destructive fires, and bed-wetting beyond 5 years of age showed a trend toward significance (chi-square analysis, $p<.10$), suggesting the possibility that the triadic behaviors are linked. Separation from a father figure longer than 6 months and presence of an alcoholic father figure also discriminated the animal cruelty group.

In summary, both the animal cruelty group and the noncruelty assaultive group gave histories of impulsive and aggressive behaviors in childhood. Parental brutality was commonly reported in both groups. In contrast to the noncruelty subjects, the men with histories of animal cruelty tended to have absent or emotionally unavailable father figures. It was hypothesized that the combination of parental brutality and lack of a stable father figure may affect a boy's psychological development in a manner that is qualitatively different from the effect of either brutality or deprivation alone.

We believe that the most comprehensive retrospective study of cruelty to animals to date was one conducted by us (28, 29). Using previously reported studies for guidance, we began our study with several assumptions. First, repeated acts of serious cruelty to socially valued animals (e.g., dogs) are more apt to be associated with violence toward people than are isolated acts of cruelty, minor abuses, and victimization of less socially valuable species (e.g., rats). Second, if animal cruelty is associated with aggression against people, it is most likely associated with serious, recurrent personal violence. A single violent offense or act would not identify this core population with continuous aggression. Third, subjects must be interviewed directly because prison records and other documents do not contain systematically gathered and adequately detailed historical data. Fourth, if a positive history of cruelty to animals exists, it will most likely be elicited by inquiry into a number of areas wherein animal involvement is possible. One or two questions on cruelty to animals do not sufficiently tap the history of an individual's involvements with animals.

Looking for samples that would include a sizable

number of recurrently aggressive subjects, we turned to U.S. penitentiaries in Connecticut and Kansas. Prison counselors were asked to rate their assigned prisoners on a scale of aggressiveness from 1 to 10. The aggressive behaviors rated on this scale included threatening speech, preparatory behaviors, and violent acts. High scores reflected the combination of frequent, severe, and multiform aggressive behaviors and, therefore, violence that was both recurrent and impulsive. Only those subjects with extremely high or low scores were asked to participate in this study. The ratings were never shared with the subjects and were communicated to the interviewers only after the interviews were completed. In addition to these objective measurements, the most violent subjects themselves confirmed that they had been recurrently and impulsively aggressive toward others. In addition to the prisoners, randomly selected young men in New Haven and Topeka were interviewed as noninstitutional control subjects. Of the 152 men who participated in this study, 32 were aggressive criminals, 18 were moderately aggressive criminals, 52 were nonaggressive criminals, and 50 were noncriminals.

A standard interview schedule with over 440 closed- and open-ended questions was administered to each subject. The interview items pertained to antisocial behaviors, environmental background, and various aspects of animal involvements, such as owning family pets, raising livestock, training animals, trapping and hunting, and attending dog, cock, or bull fights. The subjects were asked about 16 specific types of animal cruelty. A closed-ended survey on attitudes toward animals was administered. For each subject who consented, a parent or family member who knew him in childhood was contacted and interviewed.

Rigorous statistical analysis showed a significant association between acts of cruelty to animals in childhood and serious, recurrent aggression against people as an adult ($\chi^2=30.56$, df=9, $p<.005$) (28). From the responses to the closed-ended questions it was found that 25% of the aggressive criminals (N=8) had abused animals five or more times in childhood. In contrast, the figure for the nonaggressive criminals was 5.8% (N=3) and for noncriminals it was 0%.

In the second part of the study, the investigators identified the subjects in all four groups who had a pattern of substantial animal abuse in childhood, specifically, "a pattern of deliberately, repeatedly, and unnecessarily hurting vertebrate animals in a manner likely to cause serious injury" (29). Of the 20 prisoners who gave this history, 16 belonged to the most aggressive group, whereas only four fell into the nonaggressive category. Three of the 50 nonprisoners had shown a pattern of animal cruelty. With only a single exception, all animal cruelty subjects in the nonaggressive criminal and noncriminal groups had been more pugnacious toward people than one would expect from group assignment alone. A history of substantial animal abuse in childhood showed a statistically significant association with the recurrent, impulsive violence of the most aggressive sample ($\chi^2=37.2$, df=3, $p<.005$) (29).

The extensive qualitative data on animal cruelty obtained by directly administering a comprehensive interview to each subject allowed us to suggest a tentative classification of motivation for animal cruelty (28). Other interesting findings were derived from this study, but the important point is that the most thorough retrospective study of animal cruelty to date found a firm relationship between cruelty to animals during childhood and later recurrent violence against people regardless of whether the control group comprised nonaggressive prisoners or randomly selected nonprisoners.

DISCUSSION

At first glance, one might review the discrepant results of the various studies and conclude that a relationship between cruelty to animals in childhood and later personal violence has not yet been demonstrated. There were more controlled studies, involving more investigative teams, that failed to find an association than controlled studies that did. Upon closer examination, factors can be identified that probably contributed to the apparently contradictory findings.

The first consideration is definition of the behaviors studied. The definition of animal cruelty can be broadened to the point where it is essentially normative. For example, swatting at house flies or disciplining a pet dog with a gentle slap are presumably common. A vague definition of cruelty, or no definition, allows for inclusion of these and other behaviors that may not be particularly symptomatic of abnormal aggression. Most studies, particularly those that did not find an association, did not define the behavior.

Even more important is the definition of personal aggression. Violence against people occurs in many forms. We postulate that repeated acts of animal cruelty are associated with personal violence which is serious and recurrent. Recurrent violence may result in death, but not necessarily. A single violent act, threat, or attempt is insufficient to identify recurrent violence, and too many measures of violence may cloud the recurrent nature of aggression. With the possible exception of Climent et al.'s 1972 study (15), investigators who identified recurrent impulsive violence found an association with animal cruelty.

In attempting to understand discrepant findings, one must consider the various methods of data collection. Over half of the studies that found no association between childhood cruelty to animals and later violent or deviant behavior used the chart review method of data collection rather than direct interview of subjects (table 1). All studies that found an association between animal cruelty and personal aggression obtained data by means of interviewing the subjects directly (table 2). Investigators who relied only on written material cannot know whether every subject was systematically

queried about cruelty to animals and other historical variables. Having used both methods, at both hospital and prison facilities, one of us (A.R.F.) has found that even the most comprehensive clinical records do not uniformly contain adequate historical information.

Those who favor the chart review method reason that data obtained only for clinical purposes is less apt to be prejudiced than data obtained through interviews by investigators or their research assistants. On the contrary, there is no reason to believe that recording clinicians cannot be equally biased; they may exercise considerably more discretion regarding what questions to ask and what information to record than interviewers who are bound by predesigned investigative procedures.

Another factor that can account for discrepant results is variation in the thoroughness of the interviews. An interview schedule that taps several major life areas in which animals may be involved is more apt to elicit acts of cruelty in an individual's past than a schedule with just a few questions on animal cruelty.

If a pattern of animal abuse in childhood is associated with recurrent, impulsive violence toward people that continues into childhood, is animal abuse an early sign of antisocial personality disorder? A number of fine studies on delinquency or "sociopathy" (30–33) did not systematically look for a history of animal cruelty, so variables that were untested in the classic studies of criminal behavior are not widely accepted as correlates of antisocial personality disorder or recurrent aggression. Although Bowlby's writings do not indicate that he systematically investigated cruelty, he observed, "Cruelty to animals and other children is a characteristic, though not common, feature of the affectionless psychopath" (30, pp. 79, 80).

Prediction of a single act (e.g., homicide) on the basis of a preceding act (e.g., animal abuse) would be risky indeed. However, further acts of cruelty can be reasonably expected in a child who has already demonstrated an ongoing pattern of animal cruelty. In addition, although an isolated violent act in an overcontrolled individual would be difficult to predict, one could say that someone with a pattern of repeated assaults is more likely to commit assault again than someone who has never committed assault. Different patterns of aggressive behaviors also appear to be associated in many individuals. The literature suggests an association between a pattern of cruelty to animals in childhood or adolescence and a pattern of dangerous and recurrent aggression against people at a later age.

Further research on this aspect of human aggression is certainly indicated, but replication studies must apply the minimal methodological rigor suggested here lest findings serve only to confuse rather than clarify the issue. Replication studies should adopt the direct interview method of data collection. A few questions on animal cruelty are not enough. Studies should endeavor to obtain a comprehensive history of animal involvements in childhood. Identification of violent individuals based on a single act misses the point. The nature of the violence in question is *recurrent,* dangerous aggression against people. An interesting question for future investigation is whether motivation for recurrent animal cruelty correlates with motivation for recurrent personal aggression (e.g., revenge, sadistic pleasure).

Meanwhile, clinicians, jurists, school teachers, parents, and others who work and play with children should be alert to the potentially ominous significance of this behavior in childhood and the advisability of concerned, helpful intervention. Also, on a preventive note, if aggression to animals can become generalized to involve humans, perhaps an ethic of compassion and respect for animals can also carry over to humans.

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The Vermont Longitudinal Study of Persons With Severe Mental Illness, I: Methodology, Study Sample, and Overall Status 32 Years Later

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The authors report the latest findings from a 32-year longitudinal study of 269 back-ward patients from Vermont State Hospital. This intact cohort participated in a comprehensive rehabilitation program and was released to the community in a planned deinstitutionalization effort during the mid-1950s. At their 10-year follow-up mark, 70% of these patients remained out of the hospital but many were socially isolated and many were recidivists. Twenty to 25 years after their index release, 262 of these subjects were blindly assessed with structured and reliable protocols. One-half to two-thirds of them had achieved considerable improvement or recovery, which corroborates recent findings from Europe and elsewhere.

(Am J Psychiatry 1987; 144:718–726)

Understanding of the long-term course and outcome of patients with prolonged psychiatric disorders is often thwarted by patient and clinician mobility (1, 2), short-term caseloads shaped by academic training and service delivery systems (3, 4), the magnitude of methodological hurdles (5–13), and disputes over the classification of the disorders under study (10, 14–16). These conditions have produced sporadic, contradictory data and untested assumptions that undercut attempts to clarify the nature of psychiatric illness, erode the ability to target treatment interventions, and muddle efforts toward comprehensive public policies.

It is possible, however, to generate a longitudinal study that overcomes most of these obstacles (7, 17). What is required is an intact cohort of patients, selected for the established chronicity of their illness, who are prospectively followed over many years, with careful record keeping, structured and reliable protocols, operational definitions, and standardized assessments of psychopathology and psychosocial functioning. The Vermont longitudinal study meets these criteria.

Since the early 1950s, members of the Vermont Longitudinal Research Project have been prospectively following the course of an intact cohort of 269 patients from the back wards of Vermont State Hospital (7, 17–26) in much the same manner as the catamnestic studies of Manfred Bleuler at Burghölzli Hospital in Switzerland (27–33). Known in the literature as *The Vermont Story* cohort (26), the majority of these once profoundly ill, severely disabled, long-stay patients came from the sickest group in the hospital and met the *DSM-I* guidelines for the diagnosis of schizophrenia. They participated in an innovative pioneering rehabilitation program and were released to a hospital-run comprehensive community aftercare program between 1955 and 1965 (26).

Ten years after the inception of the program, we conducted a follow-up study, which indicated that two-thirds of the cohort were not hospitalized but were being maintained by heavy expenditures of clin-

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Supported by NIMH grants MH-29575, MH-40607, and MH-00340 and by Biomedical grant SO705429 from the College of Medicine, University of Vermont.

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ical effort, time, and money (34). Many of these patients were socially isolated while living and working in other institution-like settings. This follow-up period was similar to that charted by many longitudinal studies of similar patient groups, studies that have heavily influenced our ideas about the long-term course and outcome of people with severe and prolonged psychiatric disorders. The Vermont study and other longer studies provide evidence that some psychiatric illnesses require longer time periods to acquire a more complete and accurate picture of course and outcome.

In our effort to reassess the outcome of the Vermont cohort over a longer period of time, we were able to account for all but seven members of the original cohort (97%) in the early 1980s. This situation gave us the opportunity to find out whether these subjects were still as disabled as they had been 20 or more years earlier. We conducted both a structured cross-sectional assessment of the subjects' current status across a wide range of characteristics and a retrospective documentation of what had happened to members of this cohort in the intervening years. Adding these new data to the prospectively gathered information from the earlier hospitalization and rehabilitation program, we have been able to provide a more comprehensive picture of the long-term course of schizophrenia and other severe psychiatric disorders.

The specific focus of this report from the Vermont Longitudinal Research Project is a description of the sample, methodology, and design of the project and documentation of the long-term outcome for the cohort as a whole. A companion paper in this issue of the *Journal* examines the long-term outcome of those subjects within the larger cohort who were rediagnosed as meeting the newer *DSM-III* criteria for schizophrenia (35).

HISTORY OF THE PROJECT

Phase I: The Rehabilitation Program in the 1950s

In the early 1950s, one of us (G.W.B.) began to study the efficacy of the then-new drug chlorpromazine (36). The back-ward "hopeless cases" were chosen as subjects. Some patients responded well and were eventually released. Other patients did not respond as well, but the effect of the releases was to give fresh hope to both the staff and the patients. In 1955 a multidisciplinary clinical team, sponsored by the Vermont State Hospital and the Vocational Rehabilitation Division of the Vermont State Department of Education, initiated a program of comprehensive rehabilitation and community placement for those back-ward patients who had not improved sufficiently with chlorpromazine. From January 1955 to December 1960, 269 patients who were considered among the most severely disabled and chronically mentally ill in the hospital were referred to the program (26). After the re-education of the staff, a program was constructed in collaboration with the patients that consisted of drug treatment, open-ward care in homelike conditions, group therapy, graded privileges, activity therapy, industrial therapy, vocational counseling, and self-help groups.

In the community treatment component, the same clinical team went into the community and established halfway houses and outpatient clinics, found job openings, made job placements, and linked patients to natural support networks. In that era of custodial care, before the advent of community mental health centers and the later deinstitutionalization movement, this comprehensive program was considered unusual and innovative.

The average age of the subjects was 40 years. The group was described by their clinical team in *The Vermont Story* as follows:

> At the time of selection, the group averaged 16 years' duration of illness with an average of ten years of total disability and six years of continuous hospitalization. The group members had from one to ten hospitalizations, with a median of about two hospitalizations each. They had completed from none to sixteen years of schooling, with a median of about nine grades. Nearly all had been declared financially incapable of paying anything for their own care, and were committed to the hospital at State expense. The group was, in other words, quite characteristic of the schizophrenic group as outlined by Hollingshead and Redlich (37). They were middle-aged, poorly educated, lower-class individuals further impoverished by repeated and prolonged hospitalizations. In addition, this group had little social support. About five out of six were single, divorced, widowed, or separated. They were seldom visited by friends or relatives, and received very few packages or letters. (26, p. 30)

At the time the subjects were selected, the research team also described their presenting disabilities and impairments:

> The patients, as a group, were very slow, concentrated poorly, seemed confused and frequently had some impairment or distortion of recent or remote memory. They were touchy, suspicious, temperamental, unpredictable, and over-dependent on others to make minor day-to-day decisions for them. They had many peculiarities of appearance, speech, behavior, and a very constricted sense of time, space, and other people so that their social judgment was inadequate. Very often they seemed to be goalless or, if they had goals, they were quite unrealistic. They seemed to lack initiative or concern about anything beyond their immediate surroundings. Because of their very low socioeconomic level and prolonged illness, they suffered from profound poverty, inadequate educational opportunities, and a very limited experience in the world.
>
> These patients also suffered a high incidence of chronic physical disabilities. Their psychomotor performance in a wide variety of tests was impaired so that their reaction times were prolonged and their ability to perform any type of skilled or precise activity was impaired. They suffered an increased incidence of many degenerative and chronic diseases, including tuberculosis and malignant tumors.

> There was a very high incidence of needs in such areas as dental care, visual corrections, and hearing aids. Many patients, especially after prolonged phenothiazine treatment, were obese. Care of the feet had been neglected. In our experience, there also seemed to be a high incidence of chronic skin disorders including eczema-dermatitis, tinea, and psoriasis. (26, p. 31)

Phase II: The 1965 Follow-Up Study

In 1965, after 5 years of the hospital-based rehabilitation program and 5 years during which the primary focus was the community component, Deane and Brooks (34) conducted a follow-up study of these patients. They found that two-thirds of the cohort could be maintained in the community if sufficient transitional facilities and adequate aftercare were provided. Seventy percent of the subjects were out of the hospital at that follow-up: 30% had been discharged and had never returned, and 40% had been readmitted at some time but had been discharged again. Of the 30% of the subjects who were in the hospital at follow-up, 20% had been readmitted and had stayed, and 10% had never been discharged. The average number of readmissions for the recidivists in the cohort was 1.98.

Other findings indicated that being female, schizophrenic, chronically ill, and married during some part of one's life were important predictors of good functioning at follow-up. Age at first admission did not predict which patients would do better. At the 1965 follow-up, most subjects were single (60%), used community care facilities primarily for socializing, had a tendency to replace the institution with sheltered employment (e.g., a job as a cook in a nursing home, with bed and board), and maintained substantial contact with rehabilitation workers.

Thus, 5–10 years after release from the rehabilitation program, 70% of the patients were out of the hospital, which was considered remarkable at the time because they had been expected to live out their lives in the hospital. However, the study concluded with a warning:

> Implicit in our findings is the fact that any plan for rehabilitation of the chronic patient be conceived as long-term, since all of our evidence suggests that the commitment necessary to the chronic mental patient has no foreseeable end, and that unless constant attention be given to the chronic patient, the end result may be simply that he is out of the hospital, but operating at a high level of inadequacy and a low level of employment. (34, pp. ii, iii)

It is at this point that most follow-up studies stop and most programs are discontinued. Thus, most of our understanding of the long-term outcome for severe mental disorder is derived from such shorter-term data. The question asked in the present study was, Do these patients still continue to display such impairment and disabilities 20 to 25 years later, as predicted earlier by our own research team?

TABLE 1. Status at 20- to 25-Year Follow-Up of 269 Chronic Psychiatric Patients in the Vermont Study

Subjects' Follow-Up Status	Total Group	Subjects Remaining After Exclusion of 22 With Organic Disorders (N=247)[a]	
		N	%
Alive and interviewed	178	168	68
Deceased; family interviewed	71	61	25
Alive; refused participation[b]	13	11	4
Could not be located	7	7	3

[a]Twenty-two subjects classified as having organic disorders according to *DSM-III* criteria at the index admission were excluded from the data analyses.

[b]Most of these subjects were interviewed and gave considerable information, but they refused to sign the forms permitting use of their data.

Phase III: The 20- to 25-Year Follow-Up Study

We recently completed our latest follow-up of the original 269 subjects. We have follow-up data on the 22 subjects with organic disorders but removed them from our ongoing analyses to make our study comparable to others in the field. Table 1 reveals the cohort's current status.

The catamnestic period of the subjects ranges from 22 to 62 years, with an average of 32 years, which makes this study one of the longest ever conducted. The subjects who were still alive at follow-up (N=168) were divided nearly evenly between the sexes (81 men and 87 women). The mean age was 59 years (range=38–83 years), with two-thirds of the group 55 years old or older. The year of birth of the subjects ranged from 1897 to 1942.

The remainder of this report focuses on the method and results of the long-term follow-up study of the subjects who were still alive and could be interviewed.

METHOD

Measures

Batteries of structured instruments were used for collecting data. They included interview schedules and record abstraction protocols.

The Vermont Community Questionnaire (VCQ) was a battery of interview instruments designed to document and assess a subject's history and functioning in a wide variety of areas across time. Fifteen established scales were combined to create the VCQ and to acquire such a data base (7). The field interviewers were blind to hospital records and diagnostic information about each subject.

The VCQ consisted of two structured interviews, each with standardized probes, ratings, and computer coding. The VCQ-cross-sectional interview (VCQ-C) assessed current status; the VCQ-longitudinal inter-

view (VCQ-L) documented retrospective data over the preceding 20–25 years.

The major areas of functioning covered by the VCQ-C were residence, work, finances, intimate relationships, family information, social support system, typical weekly activities, basic self-care, utilization of treatment/social services, contact with the criminal justice system, community involvement, degree of satisfaction, environmental stressors, competence, and psychopathology. Approximately 1 hour and 15 minutes were required to administer the interview's 135 questions. The rater section of the interview battery contained 98 additional items based on observation and other information gathered from the subjects and their environment.

The second interview (the VCQ-L) required 75 minutes and was held within 1 week of the first. The VCQ-L had 156 questions that documented status and events during the preceding 20 years in a year-by-year follow-back procedure utilizing a modified Meyer/Leighton Life Chart (38). This chart provided a graphic overview of each subject's life and was completed with a set of structured probes, codes, and protocols created for this project. The Life Chart was a large, lined sheet of paper vertically separated into years, from 1982 at the top to 1955 at the bottom, and horizontally separated into 10 outcome areas. These domains included residence, hospitalization, work, source of income, important personal relationships, deaths of important people, other life events, use of community support systems, physical health, and medications. A Life Chart was completed for each subject, who worked with the interviewer on the chart spread out on a table.

Each of the field interviewers had had 5–8 years of previous clinical experience with a range of clients who were deinstitutionalized and labeled "chronic patients" by their community mental health clinics.

A small instrument called the Verinform was designed to verify the interview information by asking a variety of informants about the subjects' current status and historical data. The Verinform was used for interviews with general practitioners, aftercare or vocational rehabilitation counselors, family, or friends—whoever knew the subject well.

The Hospital Record Review Form was designed to provide a standardized method for recording data from Vermont State Hospital records. The interview instrument known as the Psychiatric and Personal History Schedule from the World Health Organization (WHO) Collaborative Project on Determinants of Outcome of Severe Mental Disorders (39), was converted from an interview format to a standardized form for abstracting record information on psychiatric history in a systematic and structured manner. The new format maintained the coded answers but assigned them to document five different time periods: first admission, episodes between first and index admission, index admission (the admission preceding entry into the rehabilitation program—the only common denominator across all subjects and designated arbitrarily as index for research definition purposes), life history, and episodes during the years in the community after index release. In addition, the WHO signs and symptoms checklist was augmented with Strauss's Case Record Rating Scale (40), the Strauss-Carpenter Prognostic Scale (41), and the Global Assessment Scale (42). The record reviewer was blind to all outcome and interview data. She was a clinical psychologist with several years of experience with Vermont State Hospital records.

The component instruments in each battery that used the work of others had been tested extensively for reliability and validity by their originators. However, groups of individual questions from each classic scale were taken from their original context and interwoven with questions from other instruments (e.g., the questions on social relationships from all instruments were put together to make a more natural interview sequence); therefore, reliability studies of the entire VCQ and Hospital Record Review Form batteries were deemed essential.

Initially, the VCQ-C and VCQ-L interviews were each field-tested with a wide range of community people matched in age to the cohort. These consultants critiqued the appropriateness of the questions vis-à-vis their life experiences and suggested that we add questions about powerlessness, disability income, medication compliance, and the increasing number of deaths of people in their personal support systems. This strategy led to improvement in the battery's ability to tap relevant issues for people in the age ranges to be assessed and improvement in its construct validity. Changes and deletions of items honed it to the size used in the follow-up study.

Each field battery was then subjected to two sets of interrater trials (trial 1, N=21 pairs; trial 2, N=18 pairs). The sets were completed 6 months apart to test for the degree of change in raters' assessments during the intervening time period. Both raters attended a cross-sectional and a longitudinal interview for each of the test subjects. Each rater scored the interview independently, and the pairs of ratings were then compared for concordance. The kappa coefficients from the first and second sets of trials are shown in table 2.

The Hospital Record Review, with 1,800 items, was divided into its five subsections and also subjected to trials of interrater agreement between the one reviewer who left the team and the one who subsequently joined the project. Kappa coefficients ranged from .40 ($p<.01$) to .95 ($p<.001$), and all were significant.

In summary, on the basis of the evidence presented, we rendered the conclusion that these instruments were moderately reliable and contained an acceptable degree of face and construct validity.

Procedure

Each subject still living at the time of follow-up who was willing to participate was given two interviews

TABLE 2. Kappa Levels for Interrater Agreement on Trials of Instrument Batteries Given to Vermont Study Subjects

Instrument	Kappa	
	First Trial	Second Trial
Field instruments		
Vermont Community Questionnaire		
Cross-sectional		
Interview	.96[a]	.97[a]
Rater section	.50[b]	.70[b]
Longitudinal		
Interview	.96[a]	.96[a]
Rater section	.64[b]	.59[b]
Hospital Record Review Form		
First admission	.41[b]	
Episodes between first and index admission	.95[a]	
Index admission	.40[b]	
Episodes after discharge	.94[b]	
Topical life history	.67[b]	
Life Chart (experimental)	.98[a]	.78[b]

[a]p<.001.
[b]p<.01.

(approximately 1 week apart) at his or her place of residence by one of the two interviewers. In addition, two or three people who knew the subject well were interviewed in a structured protocol to verify current status and historical data. These people included relatives, general practitioners, counselors, clinicians, and friends. All but 17 subjects (10%) resided in Vermont. The subjects who lived elsewhere were interviewed with the same protocol. Strict attention was paid to the protection of patients' rights such as privacy, confidentiality, refusal, and informed consent.

Relatives, friends, and caregivers of the deceased members of the original cohort were also interviewed. A structured protocol documented the lives and the levels of functioning of these subjects until the time of their deaths. The inclusion of these data provided a more balanced view of the long-term course of severe psychiatric disorders than has been available in past studies, which have relied on data from survivors only. A separate report will be devoted to the deceased subjects.

RESULTS

This group of back-ward patients represented the most severely ill group from Vermont's only state hospital. Two to three decades after a comprehensive rehabilitation program and a planned deinstitutionalization, one-half to two-thirds of these patients were rated as considerably improved or recovered. The findings also showed a wide variation in many areas of functioning for these patients.

Demographic Data for the Cohort at Follow-Up

Fifty-one percent of the 168 subjects who were alive, did not have an organic disorder, and were interviewed had not completed high school. However, an eighth-grade education was considered to be the norm before the 1940s in Vermont (43).

Nineteen percent (N=32) of the 168 subjects were currently married, and seven percent (N=11) were widowed. Fifty-one percent (N=86) were still single, and 23% (N=39) were divorced or separated.

Eighty-eight percent of the subjects (N=148) lived in residential and rural neighborhoods rather than industrial or commercial areas. Fifty percent (N=81) lived in independent housing (house, apartment, mobile home, or rooming house), and 40% (N=64) lived in boarding homes. (This information was coded for an N of 161.) Five single middle-aged men were currently in the hospital, seven were in level II nursing homes (institutions for individuals, including the mentally retarded, who do not require 24-hour nursing care but who do require care above the level of room and board), and four were in other settings. Of the subjects receiving boarding home care, seven seemed capable of living independently, often assisting the boarding home operator and taking responsibility for management of the home. An additional 23 were actively involved in activities within the house, at the local community mental health center, or in the community and were self-motivated. Longitudinal patterns of residence revealed an average of two readmissions for the group since release from the index hospitalization. The average total length of stay was 2 years or less.

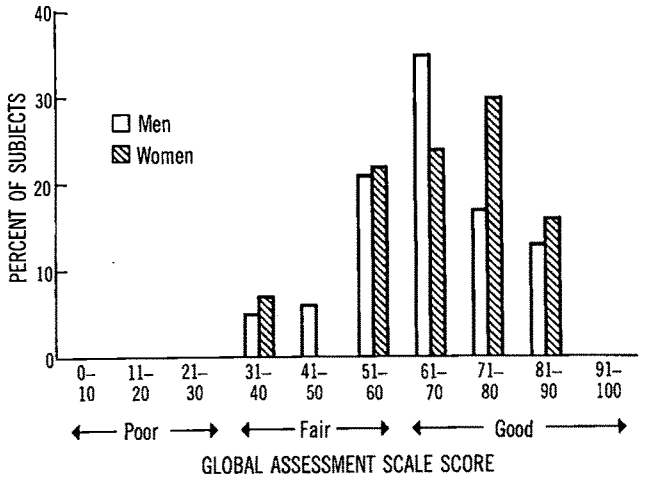
Twenty-six percent (N=44) of the 168 subjects were employed; half of them were classified as working in unskilled jobs. Thirty-three percent (N=56) were unemployed, 8% (N=14) were volunteers, and 5% (N=8) were housewives. Due to the advanced ages in the sample, an additional 26% (N=44) were classified as elderly, widowed, or retired. Solid information was unavailable on four (2%) of the subjects for this rating.

Our findings also indicated that 85% of the sample had a gross income of less than $10,000 a year. In 1982 Vermont ranked 36th in the nation for per capita income, with an average of $9,979 (44). Using an assessment from the Community Care Schedule by Schwartz et al. (45) and budget sheets outlining expenses and income, we rated 77% of the subjects as having an adequate income; the schedule's definition of adequate was that the "amount of money received will cover the subject's *basic* needs comfortably."

Overall Psychological and Social Functioning

The Global Assessment Scale (GAS) (42) was chosen to provide a single score that would capture the essence of the subjects' psychological and social functioning. Scores on this scale showed that 68% (N=114) of the study sample were functioning above the cutoff point of 61 designated by the authors as "some mild symptoms (e.g., depressive mood or mild insomnia) or some difficulties in several areas of functioning, but generally functioning pretty well, has some mean-

FIGURE 1. Global Assessment Scale Scores of 168 Subjects in the Vermont Study Who Were Alive and Were Interviewed at Follow-Up



ingful relationships and most untrained people would not consider him sick." A 2×2 (GAS by Sex) chi-square test with Yates' correction revealed no significant differences between the sexes in level of functioning (χ^2=0.13, df=1, p=.72), but it should be noted that 68% of those with a GAS score between 31 and 70 were men, while 62% of those with a GAS score between 71 and 90 were women (see figure 1).

In order to describe more of the individual components that went into the assessment of overall functioning, the Levels of Function Scale (41) was used. On this scale, subjects are scored from 0 (poor) to 4 (best) on nine items of interest; the reliability of the scale has been demonstrated. A product-moment correlation revealed that the overall total score was highly correlated (r=.88) with the GAS score just reported. Table 3 summarizes the findings from the Levels of Function Scale. Individual areas of functioning were restored for one-half to four-fifths of this group. Because of the wide variation in outcome functioning at follow-up within specific subjects, the global rating of slight or no impairment was given to only 55% (N=92) of the cohort. No impairment was rated for subjects who were asymptomatic and living independently, had close relationships, were employed or were otherwise productive citizens, were able to care for themselves, and led full lives in general. Other subjects did well in some areas of functioning but not so well in others. Theirs was a very mixed picture on a continuum weighted toward dysfunction.

TABLE 3. Results From the Strauss-Carpenter Levels of Function Scale for the 168 Subjects of the Vermont Study Who Were Alive and Interviewed

Area of Functioning	N	%
Not in hospital in past year	140	83
Met with friends every week or two	111	66
Had one or more moderately to very close friends	128	76
Employed in past year[a]	79	47
Displayed slight or no symptoms	121	72
Able to meet basic needs	133	79
Led moderate to very full life	128	76
Slight or no impairment in overall function	92	55

[a]Quality of work could not be rated; issues of confidentiality prevented visits to subjects' work sites.

DISCUSSION

Current assumptions about the long-term course of schizophrenia and other severe mental illnesses include the idea that people with repeated episodes are at best likely to achieve marginal levels of functioning over time. Heterogeneity of outcome is expected, with a dichotomized split between "process" and "reactive" patients (46), good premorbid and poor premorbid functioning (47), or type I and type II illness (48), or the familiar breakdown into "one-third get better, one-third stay the same, and one-third get worse." The findings from the Vermont cohort, drawn from the most chronically ill patients (the lowest third of the hospital), revealed that over one-half of these once profoundly ill, long-stay patients had achieved a much higher level of functioning than had been predicted by our own research team during the early days of the patients' community tenure. Their achievement is even more remarkable given their original levels of chronicity.

These findings hold for other subsets of the cohort as well. For example, our companion paper in this issue (35), about the subjects who were rediagnosed as meeting the *DSM-III* criteria for schizophrenia, describes similar proportions of restored and heterogeneous functioning, as does our forthcoming paper about the outcome of the deceased subjects before they died. Another paper will delineate the reduction by 46% of the number of individual subjects who currently use the public mental health system in Vermont. It appears that they have left the formal system and turned to natural community supports over time.

Our findings of heterogeneity of outcome, with significant improvement or recovery for half the cohort, corroborate the results of four other long-term follow-up studies conducted within the last 15 years: Manfred Bleuler's 23-year study of 208 patients at Burghölzli Hospital in Zurich (32), Ciompi and Müller's 37-year study of 289 patients in Lausanne (49), Huber and colleagues' 22-year follow-up study of 502 subjects in Bonn (50), and the "Iowa 500" study by Tsuang et al. (51). The studies from Europe have not been seriously regarded by some investigators because of such methodological difficulties as the lack of reliable diagnostic criteria, the number of deceased and missing subjects at follow-up (especially in the Lausanne and Bonn studies), and the use of less structured clinical interviews to assess psychopathology and acquire outcome data (9). However, the Iowa and Ver-

mont studies have improved on many of these methodological deficiencies, and the findings are nearly identical to those of the European studies.

Thus, of the 1,300 subjects in the five studies who were assessed two or three decades later, more than one-half were found to have considerably improved or recovered (52). Such similarities in the findings across studies seem to override the differences. Together, the data give evidence that, contrary to the expected downward and deteriorating course for schizophrenia or for other severe and chronic psychiatric disorders, symptoms can be ameliorated over time and functioning can be restored. Further support for the heterogeneity of patients' outcome functioning is supplied by many other shorter follow-up studies as well (41, 49, 53–55).

Although the Vermont Longitudinal Research Project achieved a more rigorous design than many earlier efforts, the study still has several shortcomings. In 1955, the original selection of the subjects depended on referrals of patients by the staff to the rehabilitation program. The original investigators then restricted entry into the research cohort to the most chronic patients only.

The project was primarily aimed toward establishing a treatment program to deinstitutionalize the patients remaining in the back wards. This program represented one of the first attempts at deinstitutionalization in the United States and was one of the few that was carefully planned. The study became a follow-up study as time and contacts continued. The standardization of assessments and the structured protocols were instituted as the study proceeded. Thus, the study was not initially planned as a 32-year follow-up but ended up as such.

There were no subjects who could become a control group in the Vermont State Hospital, inasmuch as the entire most severely ill third of the patients in the state's only hospital (excluding the geriatric population) was selected to participate in the program. For years an appropriate comparison sample was sought, and recently a study was undertaken in the state of Maine that matched each of the Vermont study's subjects by age, sex, diagnosis, and level of chronicity with a patient from the Augusta Mental Health Institute. These new subjects are being interviewed with the same protocols and instruments to determine their life courses and illness trajectories. The primary difference between the two samples is the presence or absence of rehabilitation efforts. It is hoped that the difference in outcome between rehabilitated and nonrehabilitated subjects will be helpful in the study of mediating factors in long-term course.

As we have noted, the Vermont subjects were selected from the most disabled patients in the hospital. We have portrayed the severity of their handicaps, the length of their institutionalization, their lack of response to phenothiazines after an average of 2½ years of psychotropic treatment, the back-ward hopeless atmosphere in which they had lived for years, the broken ties with family and community, as well as impoverished financial and educational backgrounds. In addition, many subjects behaved violently or in other unacceptable ways in their communities and were often brought to the hospital by local police. Few of these subjects used street drugs, but some abused alcohol.

Our findings should be generalizable to similar long-stay patients, estimated by Minkoff (56) and others to number about 1.1 million in the United States. The results of the study could be considered conservative for the long-term course of severe mental illness because anyone who is less severely ill, who has spent less time institutionalized, and who is less severely handicapped may have a better chance of long-term recovery. However, the use of street drugs, multiple short-term hospitalizations, and the predominance of *DSM-III* axis II diagnoses add new complexities to the current picture of prolonged psychiatric disorder, especially schizophrenia, for subgroups of younger patients; these are currently being assessed in the elegant studies of Test et al. (57) in Wisconsin.

Another aspect of the question of generalizability is whether our subjects' improvement was an artifact of the quiet, benign rural environment. Zubin (58) pointed out, "Where in the world would you get the natural history of schizophrenia if not under the best circumstances? You wouldn't want to go to the ghetto, where people are suffering from a lot of other sources of distress, to see whether the outcome is good there. You want to go to the best place, where triggering mechanisms are at a minimum" (p. 407).

The impact of rural life on the course of illness is very complex. In 1982 Vermont was a community of 518,846 people scattered in clumps across 9,273 square miles (59, 60), with a density of 56 people per square mile. Vermonters tend to pride themselves on Yankee individuality and independence (61, 62); therefore it is possible to regulate one's social distance and to find a niche sometimes for people with eccentric behaviors. Despite its ecological niches and visual beauty, however, Vermont registers fairly high rates of suicide (63), alcoholism, and incest (64), as well as unemployment, poverty, and long, difficult winters. Families and patients alike experience the pain of stigma and social rejection. Therefore, it is not clear whether the primary environment has been the deciding factor in the improvement process, but perhaps the secondary effects of a rural environment, such as small numbers and stability, have been helpful. As we said earlier in describing phase I of the project's history, the same five members of the clinical research team went with patients to the community and were available for support and clinical care over a 10-year period when the subjects were both in and out of the hospital. This continuity of contact persisted during the second 10 years, as people changed their roles from clinicians and patients to friends and neighbors. (It also may explain the 97% rate of original subjects found and the 5% refusal rate.)

Further, in any discussion of the effect of rural life, it is important to point out that the data from the Bonn and Zurich studies came from industrialized cities and that Lausanne is a medium-sized city. Only Iowa and Vermont are clearly rural localities, but the trends in the data across all five studies with different environments are similar.

The knowledge gained from our study and others that there is a wide range of long-term outcomes provides an impetus to continue the search, begun by the investigators in the three European studies, for longitudinal patterns of course of illness demonstrated by subgroups of patients who achieve considerable improvement or recovery and those who do not. Additional questions to be asked now are: When in the course of their illness did those patients who improved begin to do so? Are there any predictors of future outcome status? Many older concepts of predictors have not been as strong as once thought (32, 41, 65–67, and our companion paper in this issue), and we have begun investigations into these important questions.

The answers will begin to reshape our psychological and biological concepts of severe mental illness and the way in which service delivery systems and treatments are designed.

ACKNOWLEDGMENTS

The following people contributed to this phase of the project: design and methodology: Brendan Maher, Ph.D.; the late Robert Shapiro, M.D.; Bonnie Spring, Ph.D.; Joseph L. Fleiss, Ph.D.; Jane Murphy, Ph.D.; Joseph M. Tobin, M.D.; Lee Robins, Ph.D.; Leona Bachrach, Ph.D.; Edward Zigler, Ph.D.; Stanley Herr, J.D.; and Jon Rolf, Ph.D.; additional aid with instrumentation: William Woodruff, M.D.; Alan Gelenberg, M.D.; Gerard Hogarty, M.S.W.; Paula Clayton, M.D.; Janet Mikkelsen, M.S.W.; and Thomas McGlashan, M.D.; data collection: Paul D. Landerl, M.S.W.; Carmine M. Consalvo, Ph.D.; Janet Wakefield, Ph.D.; William Deane, Ph.D.; Barbara Curtis, R.N.; and Robert Lagor, B.A.; data management: Susan Childers, A.C.S.W.; Lori Witham; Mary Ellen Fortini, Ph.D.; Sandi Tower; Andrea Pierce; Mary Noonan; Dorothy Myer; and Joanne Gobrecht; manuscript review: Luc Ciompi, Prof.Dr.Med.; Prof. John Cooper; Boris Astrachan, M.D.; Malcolm B. Bowers, Jr., M.D.; Richard Musty, Ph.D.; George Albee, Ph.D.; Thomas Achenbach, Ph.D.; Paul Carling, Ph.D.; Lawrence Gordon, Ph.D.; and Frederick Schmidt, Ph.D.; and manuscript preparation: Nancy L. Ryan.

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The Vermont Longitudinal Study of Persons With Severe Mental Illness, II: Long-Term Outcome of Subjects Who Retrospectively Met *DSM-III* Criteria for Schizophrenia

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The authors present the findings from a long-term follow-up study of 118 patients from Vermont State Hospital who, when rediagnosed retrospectively, met DSM-III *criteria for schizophrenia at their index hospitalization in the mid-1950s. The patients were studied with structured, reliable, multivariate instrument batteries by raters who were blind to information in their records. The rediagnostic process is described, and results of the follow-up are presented. Outcome varied widely, but one-half to two-thirds of the sample had achieved considerable improvement or recovered, in contrast to statements in* DSM-III *that predict a poor outcome for schizophrenic patients.*

(Am J Psychiatry 1987; 144:727–735)

The third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III*) of the American Psychiatric Association both reflects and shapes current American thinking about the course and outcome of schizophrenia. Heavily based on the Feighner criteria (1) and the Research Diagnostic Criteria (2), *DSM-III* pictures the schizophrenic patient as a person with increasing residual impairment.

> A complete return to premorbid functioning is unusual—so rare, in fact, that some clinicians would question the diagnosis. However, there is always the *possibility* of full remission or recovery, although its frequency is unknown. The most common course is one of acute exacerbations with increasing residual impairment between episodes. (*DSM-III*, p. 185)

These impairments are said to include flattened affect, persisting delusions and hallucinations, and increasing inability to carry out everyday functions such as work, social relationships, or basic self-care. Such assumptions influence concepts of etiology (3) and course and outcome (4); in addition, they shape decisions about treatment (5), program implementation (6), economic planning (7), and social policy for mental health service delivery systems (8).

The advent of *DSM-III* has been seen by many clinicians and investigators as a major change in a field heretofore severely hampered in research and treatment relevant to schizophrenia by the lack of reliable definitions of diagnostic categories (9–11). With such a system in place (12), it is now possible to reaffirm or disconfirm the prevalent notions about the long-term course of schizophrenia.

This paper reports findings from the fifth very long-term follow-up study of schizophrenia conducted within the last decade (13–15) and the second such endeavor recently completed in the United States (16). It is the only study to date that has examined the long-term outcome of subjects rediagnosed as meeting the *DSM-III* criteria for schizophrenia.

The Vermont Longitudinal Research Project was a 32-year prospective follow-along study of a clinical research cohort (17–28). The prospectively gathered material has been combined with a systematic retrospective follow-back to document the lives of 97% (N=262) of the 269 original subjects.

In the mid-1950s, when they became subjects in the study, these patients were "middle-aged, poorly educated, lower-class individuals further impoverished by repeated and prolonged hospitalizations" (25, p. 29). Demographic, illness, and hospitalization characteristics of this cohort have been extensively described elsewhere (25–31).

The subjects were originally chosen for a rehabilitation program from the back wards of Vermont State Hospital because of their chronic disabilities and resistance to treatment. The chronicity criterion required subjects to have been disabled for 1 year before entry into the rehabilitation program. The term "disabled" was defined as inability to function in ordinary day-

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Supported by NIMH grants MH-29575, MH-40607, and MH-00340 and by Biomedical grant S0705429 from the College of Medicine, University of Vermont.

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to-day role capacities. Members of this cohort had been ill for an average of 16 years, totally disabled for an average of 10 years, and continuously hospitalized for 6 years. In addition, most patients had been given phenothiazines for 2½ years without enough improvement to warrant discharge. They were provided with a comprehensive rehabilitation program and released to the community during the mid-to-late 1950s in a planned deinstitutionalization effort (17–25, 31).

In the follow-up data collection period (1980–1982), 97% of the original cohort was extensively studied in a structured and reliable manner (30–31). The catamnestic period for these patients ranged from 22 to 62 years. More detailed descriptions of the methodology, the study sample, and the overall status of the cohort at follow-up may be found in our companion paper in this issue.

Initial results for these subjects, whose original diagnoses had been made according to *DSM-I* criteria, indicated that from one-half to two-thirds of the cohort had significantly improved or recovered (28, 30). These findings were at odds with the prevailing assumptions about the long-term course of schizophrenia. It was possible, however, that this discrepancy had been generated by the use of the loosely formulated *DSM-I* diagnostic guidelines. Therefore, with the publication of *DSM-III* while we were in the midst of our study, we undertook the task of giving a retrospective rediagnosis from case records for each of the 269 patients in order to determine what their *DSM-III* status would have been at the time they were selected for the study.

The present paper examines the process of rediagnosis and assesses the long-term outcome achieved by the group who met the *DSM-III* criteria for schizophrenia at selection. The two hypotheses involved in this aspect of the study were statements of common conceptions about schizophrenia: 1) Members of this cohort diagnosed as having met the *DSM-III* criteria for schizophrenia at index hospitalization would still have signs and symptoms of schizophrenia at follow-up. 2) Members of this cohort diagnosed as having met the *DSM-III* criteria for schizophrenia at index hospitalization would have uniformly poor outcomes in critical areas of functioning such as work, social relations, and self-care at follow-up. Confirmation of these hypotheses would lend support to the validity of the statements about the long-term course and outcome of schizophrenia that are made in *DSM-III*.

REDIAGNOSIS OF PATIENTS AT INDEX HOSPITALIZATION

Originally, 213, or 79%, of the 269 subjects had been given a diagnosis of schizophrenia according to *DSM-I* guidelines. Table 1 presents a breakdown by age, sex, and diagnosis of the entire cohort at entry into the study in the mid-1950s.

We instituted several methods to achieve the retrospective rediagnosis. First, the two raters selected (J.S.S. and A.B.) were new to the project and blind to the outcome of each subject. The raters participated in two sets of interrater trials on 40 randomly selected cases (15% of the 269 subjects), which were independently assessed in a straight series without any discussion between raters. The case records and standardized record review abstracts from the time of the patient's entry into the study were stripped of all previous diagnostic assignments as well as any information about future episodes, hospitalizations, and other outcome information after index admission. (Index hospitalization was designated as the hospitalization during the 1950s during which transfer to the rehabilitation program occurred.) The *DSM-III* criteria were strictly applied.

The hospital records had been abstracted, as part of the overall goals of the larger project, in a structured and systematic manner by means of a battery of instruments known as the Hospital Record Review Form. This battery contained forms for extracting data about family and early life history, prodromal signs, and all hospital admissions. Interrater trials had revealed it to be a reliable instrument battery (31).

For a signs and symptoms checklist, we used Strauss's Case Record Rating Scale (32) and ratings from the World Health Organization's (WHO) Psychiatric and Personal History Schedule (33). This combination battery recorded behavioral descriptors and symptom dimensions noted by the clinician in recounting his or her impressions of the patient at the time of the original assessment. Case summaries and copies of the original chart information, such as admission and discharge summaries with ward notes but with all references to diagnosis deleted, were included in each diagnostic packet. Structured *DSM-III* diagnostic checklists from WHO and the Chestnut Lodge Fol-

TABLE 1. *DSM-I* Diagnoses of 269 Chronic Psychiatric Patients at Entry Into the Vermont Study in the Mid-1950s

Diagnostic Category	Mean Age (years)	Subjects With Diagnosis (N=269)	
		N	%
Schizophrenia		213	79
Hebephrenic			
Men	36	13	
Women	41	9	
Catatonic			
Men	38	26	
Women	43	39	
Paranoid			
Men	43	48	
Women	45	59	
Undifferentiated			
Men	34	8	
Women	37	11	
Affective disorders		34	13
Men	39	16	
Women	38	18	
Organic disorders		22	8
Men	36	14	
Women	44	8	

TABLE 2. Follow-Up Status by *DSM-III* Category of 269 Chronic Psychiatric Patients in the Vermont Study Who Were Rediagnosed Retrospectively

Subjects' Follow-Up Status	Number of Subjects in Diagnostic Category						Total	
	Schizophrenia	Schizoaffective Disorder	Affective Disorders	Atypical Psychosis	Other	Organic Disorders	N	%
Alive and interviewed	82	25	29	13	19	10	178	66
Alive; refused participation	4	1	1	0	5	2	13	5
Could not be located	4	1	1	0	1	0	7	3
Deceased	28	4	16	5	7	10	70[a]	26
Total								
N	118	31	47	18	32	22	268[a]	
%	44	12	17	7	12	8		100

[a]For one patient there was not enough information to make adequate ratings.

low-up Study (34) were used by those making the rediagnoses to systematically summarize all the evidence for each diagnosis to be assigned.

Concerns about the quality of the records might be raised, because throughout the United States records from most state hospitals are considered to be poor. Vermont State Hospital's records, however, were remarkably complete. Since most of our subjects had also been the subjects of early phenothiazine drug trials before their entry into the rehabilitation program, the records tended to be of good research quality both before and during the institution of the federally funded rehabilitation program in 1957. The records described the evolution of symptoms by using statements from the patients themselves and gave examples of behaviors to illustrate the presence of hallucinations, delusions, catatonic waxy flexibility, and other symptoms. Such clinical notes were entered often by psychiatrists, residents, and other members of the treatment team. There were also mental status reports, past medical histories, results of current physical examinations, medication charts, treatment plans, progress notes, and admission and discharge summaries. In addition, social workers had collected systematic family and personal histories.

We conducted two sets of interrater trials. Complete agreement was achieved on 57% of the first 21 cases. In an analysis of the cases about which there was disagreement, it was found that 56% of the time, the second diagnosis proposed by one rater agreed with the first diagnosis selected by the other rater. Each rater agreed with the eventual consensual diagnosis 71% of the time overall and 75% of the time for schizophrenia. In assessing the level of interrater agreement, after collapsing the data into four diagnostic categories (schizophrenia, schizoaffective disorder, affective disorders, and "other" disorders), we generated an overall kappa coefficient (35) for the first trial of .40 ($p=.001$) and a kappa of .40 ($p=.02$) for schizophrenia alone. In the second trial set of 19 cases, an overall kappa of .65 ($p<.0001$) was generated; the kappa for schizophrenia was .78 ($p<.0007$). Clearly, there was an improvement in levels of agreement after the raters had further experience with the records and the diagnostic system. On the basis of the variation in the observed statistic, we concluded that the kappa value fell within the range observed by Spitzer et al. (36).

After application of the *DSM-III* criteria to the entire set of cases, 118 subjects received a diagnosis of schizophrenia (see table 2).

Fifty-four percent (114 of 213) of those who were diagnosed as having schizophrenia according to the *DSM-I* guidelines retained the same diagnosis with the *DSM-III* criteria. (An additional four members of the *DSM-III* schizophrenia group were shifted from the *DSM-I* affective disorders category.) The primary shift from the *DSM-I* category of schizophrenia occurred to the *DSM-III* categories of schizoaffective disorder and atypical psychosis, not to the affective disorders category as expected from the experience of previous investigators.

The process of rediagnosis provided subtype categories for this subsample. The paranoid subtype predominated in both the *DSM-I* (50%, or 107 of 213) and *DSM-III* (61%, or 50 of 82) classification systems. The remaining subtypes included undifferentiated (17%, or 14 of 82), catatonic (13%, or 11 of 82), and disorganized (9%, or seven of 82).

METHOD

Of the 118 subjects who met the *DSM-III* criteria for schizophrenia, at follow-up 70% (N=82) were alive and were interviewed, 24% (N=28) were deceased, 3% (N=4) refused to participate, and 3% were lost to follow-up. It should be noted that these figures are nearly identical to those reported for the larger cohort in our companion paper (see table 1 in that paper).

The present paper focuses on the long-term outcome of the 82 subjects who were alive and were interviewed 20–25 years after their entry into the project, because their data were the most reliable. The catamnestic period for these subjects ranged from 22 to 59 years.

Forty-five percent of the 82 subjects who met the *DSM-III* criteria for schizophrenia at index hospitalization had been hospitalized for more than 6 years before being transferred to the rehabilitation program in the 1950s. Twenty-four percent had been in the

hospital from 2 to 6 years, and 31% had been hospitalized less than 2 years.

Demographic analysis of these 82 subjects produced the following information. The group was split evenly between the sexes (41 men and 41 women). Their ages (as of July 1, 1981, which was the midpoint in the data collection period) ranged from 41 to 79 years. It should be noted that 91% (N=75) were above the age of 50; the average age for the group was 61 years. Fifty-five percent (N=45) of the subjects had not completed high school. Sixty-two percent (N=51) had never married, and only 10% (N=8) had remained married. Seventy-six, or 93%, were living in Vermont.

To carry out the follow-up study, our raters conducted two structured and reliable field interviews with each subject to ascertain current status and longitudinal patterns of community tenure. The raters were blind to previously recorded information about the subjects. Additional informants who knew each subject well were also interviewed, and ratings were verified. The six subjects who were not living in Vermont were interviewed with the same protocols. Another structured protocol (the Hospital Record Review Form, described at length elsewhere [31]) was used by a rater blind to all field information to abstract hospital and vocational rehabilitation records.

We used two structured interview batteries from the Vermont Community Questionnaire (30, 31), which included 15 standard scales and schedules, to assess the subjects' levels of functioning in a variety of areas at follow-up and to discern longitudinal shifts and patterns across the 20–25 years since the rehabilitation program began. All batteries were subjected to two sets of interrater trials 6 months apart and were found reliable (30, 31).

As part of the assessment, the two interviewers, who were new to the project and who had 5–8 years of clinical experience each, made ratings that provided a current clinical profile for each subject. The interviewers were blind to diagnostic record information when they made these symptom ratings, after the third hour of contact with each subject. The interviewers used the Research Diagnostic Criteria Screening Interview (36, 37), the Brief Psychiatric Rating Scale (38), and a reduced version of the Mini-Mental State examination (39) to make their assessments. This assessment package was designed to replace the Schedule for Affective Disorders and Schizophrenia (SADS) (40), proposed in our original design (27), because the extra time and costs required for the SADS interview were not funded.

In addition, the Global Assessment Scale (GAS) (41, 42) provided a single score (from 0 to 100) based on level of symptoms and social functioning. The scale's developers divided scores on the instrument into three categories (0–30=poor, 31–60=fair, 61–100=good functioning). The interrater trials generated a Pearson coefficient of .85 ($p<.0001$) for the first set (N=20) and .93 ($p<.0001$) for the second set (N=20) on this scale alone.

The Strauss-Carpenter Levels of Function Scale (43) was used to identify some of the major components that constitute the overall level of functioning assessed by the GAS. Each of the nine items is scored from 0 (poorest) to 4 (best); they include hospitalizations, symptoms, amount and quality of friendships, amount and quality of work, ability to meet basic needs, fullness of life, and overall level of functioning. (We excluded quality of work because, unlike all the other assessments, it could not be cross-checked by separate informants. A visit to each subject's work site was not deemed to be in the best interests of our subjects, most of whose employers might have been unaware of their early history as state hospital patients.) The results of interrater trials on this instrument alone generated Pearson coefficients of .92 ($p<.0001$) on the first set (N=21) and .92 ($p<.0001$) on the second set (N=18).

RESULTS

For one-half to two-thirds of these subjects who retrospectively met the *DSM-III* criteria for schizophrenia, long-term outcome was neither downward nor marginal but an evolution into various degrees of productivity, social involvement, wellness, and competent functioning. The more stringent *DSM-III* diagnostic criteria for schizophrenia failed to produce the expected uniformly poor outcome.

The combined data from the structured instrument battery described earlier, as well as all of the clinical observations obtained in the 3-hour interview sequence, indicated that 68% of the 82 subjects who met the *DSM-III* criteria for schizophrenia at index hospitalization did not display any further signs or symptoms (either positive or negative) of schizophrenia at follow-up. Forty-five percent of the sample displayed no psychiatric symptoms at all. For another 23%, symptoms had shifted to probable affective or organic disorders. One person was rated as a probable alcohol abuser (see table 3).

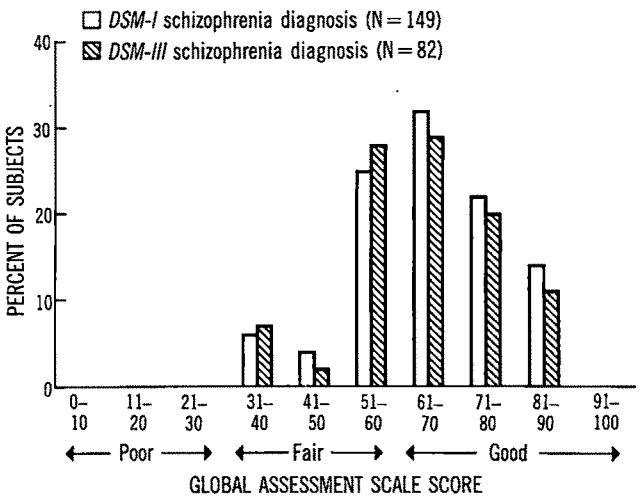
Eighty-four percent of the 82 subjects had had psychotropic medications prescribed for them; 75% of these in a low to medium dose range (in chlorpromazine equivalents). Seventy-five percent of the subjects stated they were complying with their regimes, but field interviewers were eventually told, after hours of interview time had elapsed, that the actual compliance pattern was closer to the following: about 25% of the subjects always took their medications, another 25% self-medicated when they had symptoms, and the remaining 34% used none of their medications. Adding the 34% who were noncompliers to the 16% who were currently not receiving any prescriptions for psychotropics means that 50% of the cohort was not using such medication.

A single score for psychological and social functioning was assigned each subject on the basis of the GAS. Figure 1 compares outcome scores of the subjects who met the *DSM-III* criteria for schizophrenia at index hospitalization with the scores of the subjects who met

TABLE 3. Psychiatric Status at Follow-Up of 82 Patients in the Vermont Study Originally Diagnosed as Schizophrenic and Rediagnosed According to the RDC

Diagnostic Category	Subjects With Diagnosis (N=82) N	%
No symptoms	37	45
Schizophrenia		
Positive symptoms		
Definite	1	1
Probable	7	9
Possible	0	0
Negative symptoms		
Definite	7	9
Probable	7	9
Possible	0	0
Affective disorders		
Definite	1	1
Probable	8	10
Possible	0	0
Organic disorders		
Definite	1	0
Probable	9	11
Possible	0	0
Alcoholism		
Definite	0	0
Probable	1	1
Possible	0	0
Not enough information to rate	4	4

FIGURE 1. Global Assessment Scale Scores of Subjects in the Vermont Study Who Met *DSM-I* Criteria and Those Who Met *DSM-III* Criteria for Schizophrenia at Index Hospitalization



the *DSM-I* guidelines for schizophrenia at index hospitalization. Sixty percent or more of the subjects diagnosed as schizophrenic by both diagnostic systems scored over 61, designated by the developers of the scale as good functioning. No one scored in the poor functioning category (score of 30 or less). It should be noted that all but four subjects who met the *DSM-III* criteria for schizophrenia came from the pool of subjects diagnosed as meeting the *DSM-I* criteria for schizophrenia.

FIGURE 2. Global Assessment Scale Scores of Subjects in the Vermont Study Who Met Both *DSM-I* and *DSM-III* Criteria for Schizophrenia and Subjects Diagnosed as Schizophrenic by *DSM-I* Who Had Other Diagnoses According to *DSM-III*

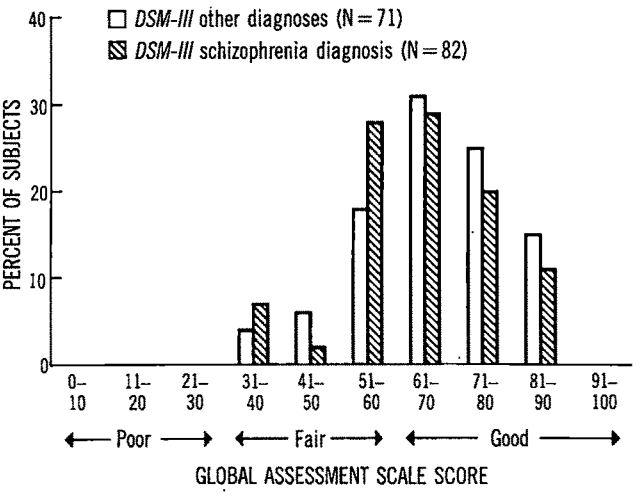


Figure 2 shows the GAS scores of the 82 subjects who met both *DSM-I* and *DSM-III* criteria for schizophrenia (including four subjects who were in other categories of *DSM-I* but who met *DSM-III* criteria for schizophrenia) and of the subjects who met *DSM-I* criteria but who were reclassified as fitting some category other than schizophrenia by *DSM-III* criteria (N=71). A t test for the means of the two groups revealed no significant differences between them ($t=-1.44$, $df=149$, n.s.).

Table 4 shows the findings from the Levels of Function Scale for living subjects originally diagnosed as meeting the *DSM-I* guidelines for schizophrenia, those for subjects who met the *DSM-III* criteria for schizophrenia, and those for subjects who met the *DSM-III* criteria for other categories. For most outcome variables in either diagnostic system, for any of the three groups, two-thirds to four-fifths of the subjects were found to be significantly improved.

The only exception to the high levels of functioning across all diagnostic categories was the rating for employment, which was scored for one-half or fewer of the subjects. However, this rating did not take into account subjects who were retired or elderly.

The major difference between the subjects who met the *DSM-III* criteria for schizophrenia and those who met the *DSM-III* criteria for other diagnoses was fewer close friendships for the *DSM-III* schizophrenia subsample (68% versus 86%) ($\chi^2=4.89$, $df=1$, $p=.03$).

We compared these two groups by using a 2×2 chi-square test with Yates' correction. A small number of cases with missing values were included in the analysis category that reflected the least positive outcome. No significant differences in results were observed when we used this approach and when we used the standard method of excluding cases with missing values.

TABLE 4. Results From the Strauss-Carpenter Levels of Function Scale at Follow-Up for Vermont Study Subjects Diagnosed as Schizophrenic by *DSM-I* and Rediagnosed by *DSM-III*

Area of Functioning	Patients With *DSM-I* Schizophrenia (N=149)		Patients With *DSM-I* and *DSM-III* Schizophrenia (N=82)[a]		Patients With *DSM-I* But Not *DSM-III* Schizophrenia (N=71)			
	N	%	N	%	N	%	χ^2 (df=1)[b]	p
Not in hospital in past year	125	84	67	82	61	86	0.23	.63
Met with friends every week or two	97	65	50	61	51	72	1.54	.21
Had one or more moderately to very close friends	113	76	56	68	61	86	5.62	.02
Employed in past year[c]	66	44	33	40	37	52	1.71	.19
Displayed slight or no symptoms	104	70	56	68	52	73	0.24	.62
Able to meet basic needs	119	80	66	81	57	80	0.00	1.00
Led moderate to very full life	113	76	60	73	57	80	0.71	.40

[a]Includes four subjects who were not schizophrenic according to *DSM-I* but who were given a *DSM-III* diagnosis of schizophrenia.
[b]Chi-square with Yates' correction for the comparison between the group diagnosed as schizophrenic by both *DSM-I* and *DSM-III* and the group with *DSM-I* schizophrenia only (now *DSM-III* other categories).
[c]Does not account for subjects who were widowed, retired, or elderly.

DISCUSSION

Members of the Vermont cohort were once profoundly ill, back-ward, chronic patients who were provided with a comprehensive rehabilitation program and released to the community 20–25 years ago. The 5- to 10-year follow-up study found that two-thirds of these patients were out of the hospital but were expected to require continuous support by the mental health system in order to remain in the community (44). Further, the subsample of this group rediagnosed as having met the *DSM-III* criteria for schizophrenia at index hospitalization would be expected, according to that system's description of schizophrenia, to have a course with "increasing residual impairment between episodes" (*DSM-III*, p. 185), including continued symptoms, unemployment, social isolation, and inability to care for themselves.

Data from the present study demonstrated that these predictions were inadequate for the majority of subjects. Widely heterogeneous patterns of social, occupational, and psychological functioning evolved over time for these once schizophrenic patients. The more stringent diagnostic criteria of *DSM-III* failed to predict any better than the more loosely formulated *DSM-I* guidelines the true outcome for these schizophrenic patients.

Although these findings show some robustness, they come from a study that suffers from numerous flaws (see our companion paper in this issue). Although it was one of the more rigorously designed research studies of its type, the selection was biased toward the long-term institutionalized patient. The use of reliable, structured instrument batteries was a significant advance over many earlier studies, but the *DSM-III* diagnoses had to be made retrospectively. The updating of subjects' diagnoses to meet current diagnostic criteria is a problem common to all longitudinal studies. It is always a trade-off to try to second-guess the original clinician, who was able to see and interact with the patient. The original clinicians were apt to neglect noting signs and symptoms that were not present and to present data to substantiate their own diagnostic decisions. We were fortunate to have excellent records rich in descriptive passages of actual conversations and behaviors to aid in our own rediagnostic work, but we did not see the patients in person then.

The structured battery that determined the subjects' current functional status was solidly reliable. The two interviewers each had 5–8 years of clinical experience with caseloads of chronic patients before these investigations, and they spent several hours with each subject as well as with a variety of other informants (including other clinicians) who knew these clients or family members well.

Our findings of heterogeneity in functioning at outcome corroborate similar results from the four other long-term studies of schizophrenia that we have mentioned: the three European studies by Bleuler (15), Ciompi and Müller (13), and Huber et al. (14) and the Iowa 500 study (16). These studies have been extensively analyzed by us elsewhere (45). Diverse levels of functioning have been found also in shorter-term studies such as the WHO International Pilot Study of Schizophrenia (33, 46), the Rochester First Admission Study (47), the Boston State Hospital 12-Year Follow-Up Study (48), and the New York State Psychiatric Institute Diagnostic Study (49).

It has been argued that the more stringent the criteria, the better a sample will reflect "true" or "core" schizophrenia (50, 51), and that core schizophrenia has a uniformly poor outcome (5, 52–54). The rigorous inclusion/exclusion criteria of the *DSM-III* classification were designed to select for core schizophrenia, but since the findings of this study revealed outcome to be heterogeneous, the *DSM-III* criteria did not predict long-term outcome as well as expected. This finding was recently duplicated for prediction of very short-term outcome as well (49).

Hawk and associates (55) also found that narrowness of criteria did not predict homogeneous outcome

functioning when they compared subjects rediagnosed according to four diagnostic systems, i.e., Langfeldt's criteria (51), Schneider's first-rank symptoms (56), *DSM-II*, and the Flexible System (57).

The focus on strictness of criteria evolved from the Kraepelinian notion that prognosis confirmed diagnosis (58). This theory stated that poor outcome reflected a unifying common denominator for clustering several differently expressed types of mental disorders under one umbrella, dementia praecox. If the patients recovered or improved, they had obviously been misdiagnosed, and another label was applied, such as reactive psychosis (59), schizophreniform states (51), or cycloid psychoses (60–61). In pursuing this argument further, Vaillant (62) cited 16 major attempts to reclassify "remitting schizophrenics" and concluded that most investigators were describing a blend known as Kasanin's schizoaffective disorder (63). Thus, there was no definitive system to describe schizophrenic patients who improved without recategorizing them as having another disorder.

A decade later, in 1975, Vaillant himself completed a 10- to 15-year follow-up of 51 patients who exhibited the classical profile of remitting schizophrenia, as cited from the literature by Stephens (64) and others. This profile included a positive family history of affective disorders, sudden onset with the patient reacting to a clear precipitant, bipolar-like symptoms, and remission within the first 2 years. Thirty-nine percent of the 51 study subjects developed a chronic course. Vaillant found no factors that could differentiate between the patients who would relapse and those who were later rediagnosed as having an affective disorder (65). He concluded that "diagnosis and prognosis should be treated as different dimensions of psychosis" (G.E. Vaillant, paper presented at the 128th annual meeting of the American Psychiatric Association, Anaheim, Calif., May 5–9, 1975).

In the current study, it should be noted that the 25 interviewed patients who were rediagnosed as schizoaffective, the three who had schizophreniform disorders, and the 13 who had atypical psychoses were all eliminated from the analyses that were done to determine the long-term outcome of "core" schizophrenia. These patients were considered to have a much better chance for a good long-term outcome. Despite this very stringent approach, there were still "core schizophrenics" who remitted—a finding that supports Vaillant's concept of the separate contributions of diagnosis and prognosis to long-term outcome (65, and the paper presented at the APA annual meeting).

In addition to incorporating the Kraepelinian idea that future course validates the original diagnosis, *DSM-III* was based on the Feighner, or St. Louis, criteria (1), which established the validity of a diagnosis by requiring deterioration from a previous level of functioning as well as a 6-month duration of illness with or without prodrome. Thus, in the *DSM-III* attempt to select out reactive, schizophreniform, and cycloid types, subjects are required to have been functioning poorly before they are entered into the classification and are expected to be functioning poorly at follow-up. Strauss and Carpenter (66) pointed out the tautology of such a scheme. They suggested that finding an outcome of chronic illness may be primarily related to the original selection of patients with a longstanding disorder as the entry criterion. However, the Vermont subjects were selected for their strong indications of chronicity (e.g., at selection these subjects had had an average of 6 years of continuous psychiatric hospitalization and 16 years of illness before entering the rehabilitation program). Despite this status, many of these very chronic patients appear to have recovered or improved considerably. This finding clearly supports those of the Bonn, Lausanne, Iowa, and Burghölzli studies, which found improvement or recovery two to three decades later (13–16).

One of the complications in analyzing data across earlier studies was the fact that those studies often used the criteria "recovered" or "improved" without defining either concept and commonly used only a single measure of outcome, such as "hospitalized" or "discharged" (see Shapiro and Shader [67] for a discussion). However, the work of Strauss and Carpenter (43, 68, 69) and many others has clearly demonstrated the partial independence in level of functioning at outcome in a variety of areas such as work, social relationships, symptoms, and hospitalization. In Strauss and Carpenter's "open-linked systems" approach (66) to analyzing the course of disorder, the best predictor of follow-up functioning was pre-episode functioning in the same area (e.g., previous levels of work predicted current levels of work—a finding also supported by Brown et al. [70] and Monck [71]). Strauss and Carpenter pointed to the need for separate measurements of functioning in a wide variety of areas.

The Vermont Longitudinal Research Project found evidence to support this strategy. Within the middle range of outcome, there were subjects in the sample who were considered to be functioning well (e.g., working, with good family relationships and friends) but who still had delusions or hallucinations. Many subjects had learned either to devise ways of controlling their symptoms—an ability reported also by Breier and Strauss (72)—or had learned not to tell anyone about them anymore. Other subjects were working but were otherwise socially isolated. Some subjects had warm and extensive social networks but did not work. The picture was a complex and heterogeneous one.

Because narrowness of diagnostic criteria seems not to predict outcome, attention might be refocused on an analysis of this hidden underlying heterogeneity within samples (28, 73) in order to sort out other possible predictors of long-term outcome.

The implications of the findings from the Vermont cohort are many and varied. The present study provides strong evidence for the limited usefulness of the current diagnostic classification systems in predicting accurately the long-term outcome for people who meet

the criteria for schizophrenia. Further, in each of the five major studies conducted in the past decade that assessed the long-term outcome of schizophrenia, one-half or more of the subjects had recovered or considerably improved in their functioning. Together, these findings offer an argument for a shift in our thinking about the proportions of schizophrenic patients who are able to achieve a better outcome than has heretofore been expected.

ACKNOWLEDGMENTS

The following people contributed to this phase of the project: design and methodology: Brendan Maher, Ph.D.; the late Robert Shapiro, M.D.; Bonnie Spring, Ph.D.; Joseph L. Fleiss, Ph.D.; Jane Murphy, Ph.D.; Joseph M. Tobin, M.D.; Lee Robins, Ph.D.; Leona Bachrach, Ph.D.; Edward Zigler, Ph.D.; Stanley Herr, J.D.; and Jon Rolf, Ph.D.; additional aid with instrumentation: William Woodruff, M.D.; Alan Gelenberg, M.D.; Gerard Hogarty, M.S.W.; Paula Clayton, M.D.; Janet Mikkelsen, M.S.W.; and Thomas McGlashan, M.D.; data collection: Paul D. Landerl, M.S.W.; Carmine M. Consalvo, M.Ed.; Janet Wakefield, Ph.D.; William Deane, Ph.D.; Barbara Curtis, R.N.; and Robert Lagor, B.A.; data management: Susan Childers, A.C.S.W.; Lori Witham; Mary Ellen Fortini, Ph.D.; Sandi Tower; Andrea Pierce; Mary Noonan; Dorothy Myer; and Joanne Gobrecht; manuscript review: Luc Ciompi, Prof.Dr.Med.; Prof. John Cooper; Boris Astrachan, M.D.; Malcolm B. Bowers, Jr.; M.D.; Richard Musty, Ph.D.; George Albee, Ph.D.; Thomas Achenbach, Ph.D.; Paul Carling, Ph.D.; Lawrence Gordon, Ph.D.; and Frederick Schmidt, Ph.D.; and manuscript preparation: Nancy L. Ryan.

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Maternal Affective Disorders, Illness, and Stress: Risk for Children's Psychopathology

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Stressful circumstances that covary with maternal affective disorder may account for some of the risk to children for psychological dysfunction. Children (ages 8–16) of mothers with unipolar or bipolar disorders were compared with children of mothers who had chronic medical illness and children of normal mothers. Comparisons included Kiddie-SADS (Schedule for Affective Disorders and Schizophrenia) diagnoses and evaluations of behavior problems, school functioning, and social competence. Compared to the other groups, children of mothers with affective disorder (especially unipolar) had high rates of diagnosis. With the effects of chronic stress statistically controlled, psychosocial outcome variables showed fewer differences between groups but indicated particular impairment for children of unipolar mothers.

(Am J Psychiatry 1987; 144:736–741)

Recent advances in the understanding and assessment of depression in children have led to an increasing appreciation of its prevalence, debilitating effects, and long-term consequences (1–3). Concurrent interest in the causes and mechanisms of adult depression has stimulated efforts to understand its developmental origins as well as its social effects. These research paths have begun to converge: increasing evidence suggests that affective disorders run in families. Supporting data come not only from family genetic studies (4–5) but also from observations of the parents of depressed children.

Presented at the 139th annual meeting of the American Psychiatric Association, Washington, D.C., May 10–16, 1986. Received Feb. 18, 1986; revised Aug. 12, 1986; accepted Dec. 8, 1986. From the Department of Psychology, University of California, Los Angeles; and the Veterans Administration Medical Center, Brentwood, Calif. Address reprint requests to Dr. Hammen, Department of Psychology, University of California, Los Angeles, 1283 Franz Hall, Los Angeles, CA 90024.

Supported by a Veterans Administration Merit Review Award to Dr. Hiroto and Dr. Hammen and an award from the William T. Grant Foundation to Dr. Hammen.

The authors thank Kelly Ellis, Jean Kaufman, and Brian Zupan for their assistance and Kay R. Jamison, Ph.D., and Michael Gitlin, M.D., for their cooperation.

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Studies specifically designed to assess risk to children of parents with affective disorders are relatively recent. Despite various methodological limitations, their findings are generally consistent: children of parents with affective disorders appear to be at increased risk for diagnosable psychopathology, especially depression, as well as for impairment in social and school functioning (5–6). Existing studies have been limited, however, in assessing mechanisms of children's risk. Most have compared children of parents with affective disorders with children of non-psychiatrically-ill parents, precluding consideration of potentially critical factors associated with having a parent with an affective disorder—in particular, the impact on children of any significant, chronic disorder or stress that may interfere with parenting functions.

A few recent studies suggest that although some risk may be specifically attributable to parental affective disorder, the presence of any parental psychopathology, parental chronic illness, or other family stress may also increase the likelihood of disorder (7–10). Unfortunately, the assessment of children's outcomes has frequently been limited by the absence of 1) data from both parents and children, essential for adequate assessment (11–12), 2) child evaluations by interviewers blind to parental diagnosis, and 3) standardized diagnostic methods and criteria.

The present study was designed to investigate psychosocial mechanisms of risk among children of mothers with affective disorders, in particular the contributions to children's disorders of ongoing maternal stress that may covary with illness. Research on children of parents with affective disorders has rarely examined the influence of such stress, even though it is likely that chronic psychiatric conditions are associated, both as causes and consequences, with high levels of interpersonal, occupational, and financial disruption, which may affect children both directly and indirectly through parental reactions.

To overcome some limitations of previous research, the design includes comparisons between children of normal mothers and mothers with unipolar, bipolar, and medical illness; various areas of children's functioning are assessed through direct child and maternal interviews, testing, and teacher assessments.

This report focuses on the diagnostic and symptom status of children in the groups, in order to determine

whether parental affective disorder contributes to children's risk for particular psychopathology or impaired functioning beyond that associated with medically ill and normal mothers, and whether differences in maternal stress affect the magnitude of risk.

METHOD

Subjects

The study compares children of mothers with chronic or recurrent unipolar depression, bipolar disorder, or a chronic medical disorder (early-onset insulin-dependent diabetes or severe arthritis) and children of mothers without a history of major psychopathology or treatment. Onset of psychiatric or medical disorders was before the children's birth or in their earliest years. All families had at least one child between ages 8 and 16; the oldest and youngest in this range were studied directly.

The sample consisted of 13 unipolar mothers with 10 boys (mean±SD age=13.5±2.5 years) and nine girls (12.3±2.4 years), nine bipolar mothers with five boys (13.6±2.5 years) and seven girls (13.0±2.8 years), 14 women with medical disorders and their nine boys (12.8±2.9 years) and nine girls (12.9±3.0 years), and 22 normal mothers and their 18 boys (12.6±2.21 years) and 17 girls (10.56±1.84 years). The affective disorder mothers were recruited from inpatient facilities, outpatient clinics, and private referrals. To capture chronic rather than simply acute effects, families did not enter the project until 3 months after the mother's hospital discharge or admission to outpatient treatment.

The unipolar mothers had a mean±SD age of depression onset of 18.6±8.2 years and reported a mean±SD of 15.5±12.6 lifetime episodes of major depression (excluding three who reported "too many to count"). Eight (62%) had been hospitalized at least once for treatment of depression (mean±SD=2.1±2.3 hospitalizations). The bipolar women had a mean± SD onset age of 22.0±10.5 years and had experienced 2.2±2.5 manic episodes and 5.9±3.6 depressive episodes. They had been hospitalized 2.3±2.2 times.

Medical control mothers were recruited from specialty practices, American Diabetes Association and Arthritis Foundation newsletters, and a diabetes registry. Their mean±SD age of onset of illness was 17.4±11.1 years, and they had experienced 5.5±8.8 hospitalizations for treatment of their disorder. Thus, the group's illnesses paralleled the course of chronic affective disorder, with acute episodes and periodic hospitalizations. Several women in this group had experienced depressive or other reactions to life circumstances or their illnesses.

Normal volunteer families were recruited from the same or demographically similar schools as families in the other groups. Women responding to a project letter were screened by telephone; only those reporting no present or past treatment of psychiatric conditions were evaluated by interview. Several women had had depressive reactions to life events, corresponding to the *DSM-III* category of adjustment disorder with depressed mood.

The majority of families were Caucasian (unipolar, 69% [N=9]; bipolar, 89% [N=8]; medical, 100% [N=14]; normal, 73% [N=16]); the nonwhite families were Hispanic or black. Hollingshead two-factor scores of socioeconomic status (13) placed most families in the middle to upper socioeconomic groups (unipolar, 49% [N=6]; bipolar, 89% [N=8]; medical, 86% [N=12]; normal, 68% [N=15]), and the groups did not differ significantly on Hollingshead scores ($F=1.36$, $df=3, 51$, n.s.). The majority of women in the affective disorders groups were not currently married (unipolar, 77% [N=10], and bipolar, 78% [N=7]), whereas 29% (N=4) of the medical illness mothers and 27% (N=6) of the normal mothers were not married, a statistically significant difference ($\chi^2=10.81$, $df=1$, $p<.001$).

Procedure

Data were collected in a session with the mother alone and a session with the mother and children about 2–4 weeks later. (Data are being collected in 6-month through 3-year follow-ups and will not be reported here.)

Initial session with mother. Information about current and past psychiatric functioning was obtained with the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (14), the Beck Depression Inventory (15), and a short form of the Minnesota Multiphasic Personality Inventory, used primarily to confirm the status of the normal comparison group.

Current and past psychiatric status of the spouse and the children's biological father were assessed according to the Family History Research Diagnostic Criteria (16). A modified Kiddie-SADS (K-SADS) (12) interview was administered for child assessment.

Maternal ongoing life stress was assessed by interview at both sessions and at follow-ups. To scale the measurement of ongoing stress, seven content areas (e.g., marital/social, financial, occupational, relationships with children, relationships with other family members, physical health of self, and physical health of other family members) were rated on behaviorally defined 5-point scales for average level over the past 6 months. For example, for family relationships, 5=extremely close and supportive; 4=mutually satisfying, typical ups and downs; 3=significant conflicts, frequent arguments, but no threat of separation; 2=serious conflicts, potential abuse, or separation; 1=abuse or separation. Interrater reliability on a subsample of families ranged between .93 and .99 across content areas. Additional psychometric properties are reported in a separate study (17).

TABLE 1. Current and Past K-SADS Diagnoses of Children From 58 Families Whose Mothers Had Unipolar, Bipolar, or Medical Illness or Were Normal

Variable	Families Whose Mothers Had Unipolar Illness (N=13)		Families Whose Mothers Had Bipolar Illness (N=9)		Families Whose Mothers Had Medical Illness (N=14)		Families Whose Mothers Were Normal (N=22)	
	N	%	N	%	N	%	N	%
Families with at least one child diagnosed	11	85	9	100	8	57	8	36
Families with one child with affective disorder[a]	10	77	3	33	4	29	4	18
Children who were directly studied	19		12		18		35	
Diagnosis[b]								
Affective disorders	14	74	8	67	8	44	6	17
Major depression	9	47	3	25	3	17	3	9
Minor depression	7	37	5	42	5	28	4	11
Dysthymic	6	32	1	8	1	6	1	3
Hypomanic	0	0	0	0	0	0	0	0
Behavior disorders	7	37	4	33	2	11	3	9
Attention deficit	2	10	1	8	1	6	2	6
Aggressive conduct	4	21	1	8	0	0	3	9
Unaggressive conduct	5	26	3	25	1	6	1	3
Drug abuse	5	26	0	0	1	6	1	3
Alcohol abuse	1	5	1	8	1	6	1	3
Other emotional disorders	6	32	6	50	3	17	4	11
Separation anxiety	3	16	3	25	2	11	3	9
Overanxious	1	5	1	8	2	11	1	3
Conversion	1	5	0	0	0	0	0	0
Simple phobia	0	0	1	8	0	0	0	0
Obsessive-compulsive	0	0	0	0	0	0	1	3
Unspecified nondepression	2	10	1	8	0	0	1	3
Any diagnosis	14	74	11	92	9	50	10	29
No diagnosis	5	26	1	8	9	50	25	71
Treated for any disorder	9	47	6	50	5	28	5	14
All children in the family[c]	26		19		32		57	
Hospitalized for any disorder	8	31	1	5	0	0	1	2

[a]Minor depression excluded.
[b]Percentages within groups do not total 100% because children may have had more than one diagnosis.
[c]Includes children who were directly studied and their siblings (N=134).

Family session with mother and children. The mother completed the Child Behavior Checklist (CBCL) (18), generating subscores of behavioral symptoms and social competence for each child. Child interviews using the K-SADS assessed current and past diagnoses of childhood disorders. Interviewers were initially blind to the mothers' diagnostic status, although occasional spontaneous remarks by children precluded complete blindness. Diagnostic reliability evaluated on a subsample of 35 children independently rated by a second judge yielded a kappa coefficient of .84 ($p<.001$) on current diagnosis and 96% exact agreement on scale ratings of symptom severity. The research team combined data elicited from the child and the mother to arrive at the final diagnoses.

Current mood was assessed with the self-report Children's Depression Inventory (19). Other cognitive-emotional variables were assessed and mother-child interactions observed; these will be described in a forthcoming report.

School behavior was assessed by child, mother, and teacher reports. Because of variation across schools, ratings of academic performance and behavioral functioning were made on the basis of all available data using two 5-point scales. A rating of 1 indicated serious problems (grade failure, expulsion); a rating of 5 indicated superior functioning. In addition, the teacher having the most contact with the child completed the Conners Teacher Rating Scale of behavior disorder symptoms (20).

RESULTS

Children's Diagnostic Status

Table 1 presents rates of current and past K-SADS diagnoses (children may have received multiple diagnoses). The groups differed significantly in presence or absence of any disorder ($\chi^2=18.88$, df=3, $p<.001$). Children in the two affective disorder groups had very high rates of diagnosis, and the medical group had lower but nonetheless moderate rates, compared with the children in the normal group. The combined affective groups differed marginally significantly from the medical group ($\chi^2=3.70$, df=1, $p=.055$) and significantly from the normal group ($\chi^2=15.87$, df=1, $p<.0001$). Similar patterns occurred for overall categories of affective, behavioral, and other emotional disorders. When the family rather than the individual child is used as the unit of measurement, the groups differed significantly ($\chi^2=14.63$, df=3, $p=.02$).

Rates of affective disorders in children were significantly higher for the unipolar and bipolar groups than for the normal group ($\chi^2=17.36$, df=2, $p<.0001$) but not in comparison with the medical group. The unipolar group children had especially high rates of major depression (nine of 19 children), compared with three of 12 in the bipolar group. Six unipolar children but only one bipolar were diagnosed *(DSM-III)* as dysthymic. Alternatively, using the family as the unit of measurement, the lower part of table 1 indicates that 77% (N=10) of all unipolar families had at least one child with significant depressive problems (major depression or dysthymic disorder), compared to only 33% (N=3) of the bipolar group children. Unipolar group children also tended to show more conduct disorder and drug use disorder. Although no children met the criteria for hypomania, four children, all in the bipolar group, had significant subsyndromal symptoms.

Rates of treatment (psychotherapy, counseling, or hospitalization) for psychological disorders (table 1) show significantly higher frequencies for children in the affective disorders group compared to the normal group ($\chi^2=7.51$, df=1, $p<.01$) but not compared to the medical group. Rates of hospitalization that include other (older) children in the family who were not studied directly are especially striking for the unipolar group. Overall, therefore, there appears to be an especially high risk to children of unipolar mothers for significant depressive disorders, alone or in combination with other disorders, requiring treatment.

The additional 27 male and 23 female offspring who were not studied directly (e.g., outside of age range, did not live with the mother) were diagnosed on the basis of maternal report only. Rates of diagnosis of affective and other emotional disorders were somewhat lower than rates based on both maternal and child interviews. Nevertheless, rates of any disorder, not shown in table 1, (unipolar, 60% [N=4]; bipolar, 57% [N=4]; medical, 44% [N=7]; and normal, 5% [N=1]) were significantly different overall ($\chi^2=36.58$, df=3, $p<.0001$), with the affective disorders groups also differing significantly ($p<.05$) from the normal group but not from the medical illness group on categories of affective, behavioral, and other emotional disorders. Additionally, an older child of a unipolar mother and one of a medical illness mother had committed suicide.

Gender and age differences in children's diagnoses. There were no sex differences in rates of diagnosis overall or within categories. Children with currently diagnosable disorders were distributed evenly across all ages. Age of onset of any lifetime disorder, as estimated by all available information, was most frequently school age (7–12 years; 60% [N=24]), followed by preschool age (0–6 years; 20% [N=8]) and adolescence (13 years and above; 20% [N=8]).

Impact of paternal disorder. Family History Research Diagnostic Criteria diagnoses were available for most of the children's biological fathers, based on maternal reports. Six of 11 fathers in the unipolar group, about whom information was available, had diagnosable disorders, and six of eight known fathers in the bipolar group had disorders. Across these two groups, five fathers were alcoholic, three had affective disorders, one was schizophrenic, two had antisocial personality disorder, and one had significant nondiagnosable symptoms. In the medical and normal groups, of 36 fathers, four had experienced depression (one was bipolar), six had a diagnosis of alcohol or drug abuse, and two had antisocial personality disorder. When both parents had disorders, children's rates of disorder were only slightly higher than they were when only one parent was ill (70% vs. 63%). However, when both parents specifically had an affective illness, children's rate of diagnosis was 80%.

Presence or absence of the biological father in the home, both when ill and when not, had little impact on children's rates of disorder. Sixty-seven percent (N=4) of children whose ill fathers lived at home had a diagnosis themselves, but so did 68% (N=19) of children whose ill father was not at home. Thirty percent (N=3) of children whose father was not ill and did not live at home had diagnoses, but so did 16% (N=5) of children whose not-ill father lived at home.

Children's Psychological Functioning

Most offspring studies present statistical comparisons between groups on outcome variables, thereby testing the implication that observed differences are due to parental pathology. However, a hypothesis of the present investigation is that stressful conditions in the family that covary with disorder may contribute to children's dysfunctions. One test of this is the inclusion of a medical illness comparison group; a more sensitive test involves statistical control of the effect of chronic stress. Analyses of covariance between groups were performed with mean maternal chronic stress across roles (excluding stress associated with parent-child relations) as the covariate to control for within-group differences in stress.

Table 2 presents the means adjusted for the effect of the covariate and indicates the results of planned contrasts between the affective disorders groups and the medical and normal groups. Table 2 also indicates significant contrasts when no control for stress was used.

Because some of the families contributed two children and thus their data are not technically independent, only one randomly selected child from each family was used in the analyses.

Children's lifetime diagnoses were converted to a continuous variable by scaling from 0 (no diagnosis) to 3 (two different major disorders, such as conduct disorder and major depression). A variable for affective diagnoses was scaled from 0 (no diagnosis) to 3 (two episodes of major depression or hospitalization for major depression).

Across the diagnostic and psychosocial outcome

TABLE 2. Adjusted Group Means on Children's Outcome Variables and Planned Comparisons of Combined Affective Disorders With Medical Illness and Normal Groups

Variable	Mother's Group				Planned Comparison	
	Unipolar Illness	Bipolar Illness	Medical Illness	Normal	Unipolar and Bipolar Illness Versus Medical Illness	Unipolar and Bipolar Illness Versus Normal
Diagnostic ratings						
Any disorder	1.9	1.3	1.1	0.9	n.s.[a]	.05[a]
Affective disorder	1.9	0.9[b]	0.9	0.8	n.s.[a]	.05[a]
Psychological functioning						
Children's Depression Inventory	7.1	5.5	4.9	5.9	n.s.	n.s.
Child Behavior Checklist–Social Competence	36.5	44.5	46.0	48.2	n.s.	n.s.[a]
Child Behavior Checklist–Behavior Problems	65.7	53.8[b]	57.0	54.3	n.s.	n.s.[a]
School and teacher ratings						
Academic performance rating	2.8	3.1	3.5	4.0	n.s.	.01[a]
School behavior rating	2.5	4.0[b]	3.6	4.0	n.s.	.01[a]
Conners teacher rating	27.6	15.0	25.8	11.6	n.s.	n.s.[a]

[a]Same contrast performed in analysis without stress covariate ($p<.05$).
[b]Post hoc t test between unipolar and bipolar group ($p<.05$).

variables there were no significant differences between the affective disorders groups and the medical control group. There were four statistically significant differences when the affective disorders groups were compared with the normal group children: the former had more diagnoses of any kind as well as affective diagnoses, and they performed less well at school both academically and behaviorally. The table also indicates that when no covariate was used to control for group differences in stress level, nine of 16 comparisons were significant, whereas only four remained significant when chronic stress was controlled.

It appeared that on most variables the children of unipolar mothers generally fared the worst, although only three of eight variables indicated a significant t test difference between unipolar and bipolar group children.

DISCUSSION

The results add to the accumulating evidence that children of parents with affective disorders are at risk for diagnosable disorders and impairment in social, behavioral, and academic functioning. The rates of lifetime disorder observed in the present sample were higher than in most similar reports (5, 6), although recent studies especially have found high rates (21, 22). Several features of the present investigation may have contributed to high levels of diagnoses: direct child interviews, which may yield higher rates than mother-only interviews (12, 21); inclusion of only women with severe, chronic, or recurrent disorders; and a sample in which many women were single and had major responsibility for child care, which may have made this an especially highly stressed sample.

Although very high rates of diagnoses in children of women with affective disorders were observed, two important qualifications need to be made. First, the risk appears to be attributable not just to maternal psychopathology but also to the concurrent chronic stress in the families, and second, rather than an overall risk for affective disorders, unipolar and bipolar groups appear to have different outcomes.

Diagnostic evaluations indicated that at least moderate rates of disorder were apparent in families of highly stressed but psychiatrically normal women. The potential role of stress is suggested by the diagnosis rates in the children of medically ill women (57% [N=8] of such families had at least one child diagnosed), and a subsample of the eight normal women with the highest levels of ongoing stress had a rate of 75% (N=6) compared with only 14% (N=2) for the remaining normal families. Further indications of a significant contribution of stress came from the analyses of covariance controlling for differing levels of chronic stress in families. Only four of 16 comparisons between the affective disorders groups and the two nonpsychiatric groups remained when stress was controlled.

The role of stress in the impairment of children at risk is poorly understood at this point. Mothers in the present sample often experienced occupational, marital, and financial problems that were either a consequence of their affective disorder, a contributor to their symptomatology, or an indistinct combination of both. The relative contributions of stress and maternal symptomatology to children's outcomes are the focus of further investigation, while the mechanisms by which stress affects children, such as its impact on maternal interactions with children, are the focus of a forthcoming analysis.

Most analyses indicated poorest functioning, most diagnoses, most affective diagnoses, and most behavioral problems in children of unipolar mothers, even when stress was controlled. Although the small sample sizes to date preclude definitive conclusions, children of unipolar mothers appear to be more impaired than children of bipolar mothers. Whether this may be due to unipolar mothers' greater impairment between ma-

jor episodes or other factors requires further investigation.

Finally, several important issues remain for further study, including analysis of the impact of paternal pathology and generational family history of disorder (although the study is limited by lack of direct assessment of biological fathers and other relatives). Longitudinal analyses will help answer questions about the timing, duration, or recurrence of disorders in children and the development of disorders or presence of protective factors in children who have not yet displayed significant symptoms.

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Changes in AIDS Risk Behaviors Among Homosexual Male Physicians and University Students

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Two samples of homosexual men, 64 physicians and 58 university students, reported profound decreases in several sexual practices linked to transmission of acquired immune deficiency syndrome (AIDS). The physicians showed the greater reduction. When sociodemographic variables, health beliefs, feeling of control over outcome, mood, sexual interest before the AIDS epidemic, and medical care utilization were correlated with decrease and/or increase in AIDS risk behaviors, the clusters of variables most strongly correlated with change in risk behaviors differed between the physicians and students. Interventions designed to change behaviors in AIDS high-risk groups should be tailored for specific subgroups.

(Am J Psychiatry 1987; 144:742–747)

Homosexual men have consistently accounted for more than 70% of the U.S. cases of acquired immune deficiency syndrome (AIDS) (1, 2). Sexual contact is a major route of AIDS transmission (1, 2). Specific sexual practices identified in univariate analyses as possible AIDS risk behaviors among homosexual men have included a high number of sexual partners (3, 4), sexual contact with an individual with AIDS or AIDS-related complex (5), a higher number of incidents of receptive anal intercourse (4, 6, 7), manual stimulation of the partner's rectum (4, 7), and swallowing the ejaculate in oral-genital intercourse (4). Multivariate analyses have indicated that a higher number of sexual partners and more incidents of receptive anal intercourse are the strongest independent correlates of seropositivity for human immunodeficiency virus (HIV) in homosexual men (8).

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The authors thank Rex Reese, Ph.D., the Southern California Physicians for Human Rights, and the UCLA Gay and Lesbian Alliance for their support and Jackie Golding for data analysis.

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HIV has been identified as the infectious agent of AIDS, and HIV antibodies have been identified in a high percentage of patients with AIDS and AIDS-related complex and members of high-risk populations (3, 7, 9). HIV has been recovered from the saliva, semen, and blood of people in these groups (10–12).

Primary prevention of AIDS through reduction in the number of sexual partners and in sexual contact involving exchange of body fluids has been recommended to control the AIDS epidemic (13–15). There appears to be a complex relationship between premorbid personality, knowledge about AIDS, perceived personal risk of contracting AIDS, and change in sexual behavior (13–16). One report (17) has documented changes in sexual behavior among gay men. Two other groups have reported decreases in high-risk sexual behaviors in gay men since the onset of the AIDS epidemic (unpublished studies by K. Siegel et al. and D.G. Ostrow et al.).

We studied two groups of well-educated homosexual men who were active members of openly gay professional or student organizations but were likely to differ on a number of variables that might be related to changes in sexual behavior among homosexual men generally. These variables of interest included the subject's age, the number of years he had identified himself as gay, his personal experience with AIDS patients, and whether or not he was in a stable relationship with a lover.

We gathered information about self-reported changes in sexual behavior, knowledge and attitudes about AIDS and its transmission, and changes in social and recreational activities in two samples of homosexual men: physician members of the southern California chapter of the Physicians for Human Rights, an organization concerned with problems faced by gay physicians and other members of the gay community, and male university students who were members of a gay and lesbian student organization.

METHOD

We designed a self-report questionnaire that assessed the subjects' knowledge and attitudes about AIDS, personal health concerns, life style changes,

perceptions of gay community concerns, demographic characteristics, social support and social network characteristics, and changes in sexual activities since the onset of the AIDS epidemic. Recent emotional state was measured with the Profile of Mood States (POMS) (18), which has six subscales from which a total mood disturbance score is calculated.

The questionnaire, the POMS, and a consent form were distributed to each subject after oral and/or written explanation of the study to potential subjects. The university student subjects (N=58) were recruited from students attending weekly meetings of the UCLA Gay and Lesbian Student Alliance or a regional conference of gay and lesbian university students that took place on the UCLA campus. These subjects were drawn from an unknown number of homosexual male university students, but presumably the number is large, as the enrollment at UCLA is approximately 30,000 and some of these subjects were enrolled at universities other than UCLA.

The physician subjects were informed about the study by the newsletter of the Southern California Physicians for Human Rights. Study packets were sent to all registered members (N=220) of this organization. The participation rate for the physicians contacted was 32.7%; 64 completed research packets were received from men, and eight were received from women. Only the responses of the gay male physicians are included in this report.

All subjects were entered into the study within 4 months in the spring of 1984. The number of students who attended meetings of the UCLA Gay and Lesbian Student Alliance but did not enter the study is unknown. No information is available concerning the demographic characteristics of the overall groups of students and physicians from which the individual study participants were drawn.

Data Analysis

The demographic characteristics assessed by group were sexual preference, age, ethnicity, religion, educational level, number of years the subject had identified himself as homosexual, and presence or absence of current significant relationship. For physicians, the year of medical school graduation and practice specialty area(s) were recorded.

POMS subscale and total Mood Disturbance scores were calculated for each subject by means of the standard scoring techniques (18). The subjects' responses to questions about the epidemiology of AIDS, the identified AIDS high-risk groups, personal knowledge of someone with AIDS, symptoms of AIDS, and risk factors for transmission of AIDS were recorded by subject group. The subjects' alterations in their patterns of social, leisure, and sexual activities since the onset of the AIDS epidemic were noted. Their own anxiety about AIDS and the anxiety they perceived in the gay community were assessed with 100-mm visual analogue scales.

The main independent variables for analysis included demographic characteristics, knowledge of AIDS, health beliefs, social network and social support characteristics, psychological distress, and number of visits to a physician in the past 6 months. Specific independent variables were included in the analyses if in either the student or physician group they were associated with the dependent variables at the .10 level or more (Pearson r) and the probability for the association was less than or equal to .10. The items that met these criteria were age, knowledge of persons who either had AIDS or had died from AIDS (range=0–2), perception of self in a high-risk group (0=no, 1=yes), perceived personal vulnerability to AIDS (range of anxiety level on visual analogue scale=0–100), agreement with the statement that it is pointless to change sexual habits because of the long AIDS incubation period (range=1–4), perception that gay men have changed their sexual practices (range=1–4), perceived level of gay community anxiety (range=0–100), interest in sex before the AIDS epidemic (range=1–4), and satisfaction with sex before AIDS (range=1–4). The social network and social support characteristics that met the inclusion criteria were living with lover (0=no, 1=yes), being able to count on lover for emotional support (range=1–4), number of friends, and number of trusted friends. POMS total mood disturbance score and number of physician visits in past 6 months were also included.

The two dependent variables, proportional decrease and proportional increase in AIDS risk behaviors, were derived from self-reports of change in 10 sexual activities considered risk behaviors for AIDS because of possible interpersonal exchange of body fluids. The 10 sexual (possible) AIDS risk behaviors studied were number of sexual partners, receptive and insertive anal intercourse, active and passive fellatio, active and passive analingus, insertive and receptive manual rectal stimulation, and deep kissing. The activities studied that were not AIDS risk behaviors included looking at pornography, hugging and touching, masturbation, and mutual masturbation. Proportional decrease in AIDS risk behaviors was calculated by dividing the number of behaviors engaged in less frequently or completely stopped by the number of behaviors engaged in before the onset of the AIDS crisis. The proportional increase in risk behaviors was calculated by dividing the number of activities engaged in more frequently by the same denominator.

All multivariate analyses were done separately for the two groups. The correlational analyses used Pearson's product-moment correlation. The prediction model was estimated by means of forward stepwise multiple regression with no variable preselection and the number of steps limited to five. Beta values (standardized coefficients) and estimates of explained variance for each step and the full model are used for interpretation of the multivariate regression. For single-variable comparisons of the physicians and students, two-tailed tests of significance were used.

TABLE 1. Demographic and Life Style Characteristics of Homosexual Male Physicians and University Students

Characteristic	Physicians (N=64)[a]		Students (N=58)[a]	
	N	%	N	%
Ethnicity[b]				
Caucasian	47	88.7	39	70.9
Non-Caucasian	6	11.3	16	29.1
Religion				
Protestant	15	24.6	7	13.0
Catholic	4	6.6	10	18.5
Jewish	17	27.9	5	9.3
Other	6	9.8	11	20.4
None/atheist	19	31.2	21	38.9
Education[c]				
Some college	0	0.0	37	63.8
Bachelor's degree	1	1.6	9	15.5
Work toward doctorate or professional degree	1	1.6	11	19.0
Doctorate or professional degree	61	96.8	1	1.7
Year of medical school graduation				
Before 1960	6	10.2		
1960 to 1969	17	28.8		
1970 to 1977	21	35.6		
1978 or after	15	25.4		
Type of medical practice				
General/family	13	20.3		
Internal medicine or subspecialty	13	20.3		
Surgery or subspecialty	7	10.9		
Psychiatry or neurology	13	20.3		
Radiology	5	7.8		
Anesthesiology	2	3.1		
Pediatrics	8	12.5		
Emergency room	3	4.7		
Living with sexual partner[d]	24	37.5	5	8.6
Sexual preference				
Homosexual	58	90.6	54	93.1
Bisexual	6	9.4	4	6.9
Have current lover	32	50.0	26	44.8

[a]Total N varies because of missing data on some variables.
[b]Significant difference between groups ($\chi^2=5.25$, df=1, $p\leq.05$).
[c]Significant difference between groups ($\chi^2=110.25$, df=3, $p\leq.05$).
[d]Significant difference between groups ($\chi^2=14.00$, df=1, $p\leq.05$).

RESULTS

Table 1 shows selected demographic characteristics of the physicians and students. The mean±SD ages of the two groups were 38.5±9.5 and 25.2±8.5 years, respectively ($t=-8.14$, df=120, $p\leq.001$), and they had been gay for a mean±SD of 18.3±11.2 and 7.8±5.8 years ($t=-6.40$, df=91.5, $p\leq.0001$). All 122 subjects listed homosexual men as a group at high risk for AIDS, and they all reported being homosexual or bisexual. A significantly higher percentage of students (31.6%) than physicians (14.1%) did not regard themselves as being members of a high-risk group ($\chi^2=5.34$, df=1, $p<.05$).

Both groups agreed that AIDS may have an incubation period of 2 years or more and did not believe that the incidence of AIDS was stabilizing. Significantly more of the physicians knew someone with AIDS (57.8% versus 19.0%; $\chi^2=19.24$, df=1, $p<.001$), and fewer of them agreed with the statement that AIDS is "nearly 100% fatal" (n.s.). More of the physicians believed that exchange of bodily fluids, a high number of sexual partners, and specific sexual acts are means of AIDS transmission, and more of them rejected the use of nitrates ("poppers") and social contact with AIDS patients as risk factors.

More of the physicians believed that other gay men had changed their sexual practices, while the students were more likely to agree with the statement that it is pointless to change sexual behavior.

The physicians had significantly higher mean POMS scores for depression ($T=-3.82$, df=72.2, Satterthwaite's approximation, $p<.001$), anger ($T=-5.61$, df=110.0, $p<.001$), and total mood disturbance ($T=-4.56$, df=63.5, Satterthwaite's approximation, $p<.001$), and a significantly lower vigor score ($T=-10.44$, df=112.0, $p<.001$) than the students.

About one-third of each subject group indicated they currently engaged in exercise more frequently. A high percentage of both groups indicated that they did not currently engage, or engaged less frequently, in recreational drug use, cigarette smoking, alcohol use, and overeating.

Before the AIDS epidemic, most subjects in both groups participated in looking at pornography, hugging and kissing, masturbation and mutual masturbation, active and passive fellatio, and anal intercourse (table 2). The marked decrease among both groups in AIDS risk behaviors and the moderate increase in behaviors not considered to increase AIDS risk suggest a sophisticated pattern of change. The physician group reported the greater reduction in AIDS risk behaviors.

There was no significant difference between these two subject groups in any of the social support categories studied.

The physicians reporting reduced AIDS risk behavior were more likely than physicians who had not to live with a lover, but they felt they lacked emotional support from their lovers. Also, they rated themselves as feeling vulnerable to AIDS, perceived themselves as being in an AIDS high-risk group, and believed that other gay men had changed their sexual practices.

The students reporting reduced AIDS risk behavior had fewer trusted friends than the students who had not reduced their risk behaviors, and were more likely to have known someone who had AIDS or who had died from AIDS. Dissatisfaction with sex before the AIDS epidemic, inability to count on a lover, and higher perceived level of gay community AIDS anxiety also correlated with reduced AIDS risk behavior.

The physicians reporting increased AIDS risk behaviors were younger, had a higher mean POMS total mood disturbance score, and were more likely to believe that it is pointless to change sexual behavior.

The students reporting increased AIDS risk behaviors had a higher level of sexual interest before AIDS, reported fewer trusted friends, and had made fewer physician visits during the previous 6 months.

The results of the forward stepwise multiple regression analyses to examine the multivariate relationship between the independent variables and the dependent

TABLE 2. Changes in Sexual Activities of Homosexual Male Physicians and University Students Since Onset of AIDS Epidemic

Change in Sexual Activity	Physicians (N=64)			Students (N=58)			Analysis	
	Number Before AIDS	After AIDS		Number Before AIDS	After AIDS		χ^2 (df=2)	p
		N	%		N	%		
Possible AIDS risk behaviors								
High number of sexual partners	62			54			11.15	.004
Increase		0	0.0		3	5.6		
No change		10	16.1		20	37.0		
Decrease/stop		52	83.9		31	57.4		
Receptive anal intercourse	51			46			6.80	.03
Increase		4	7.8		4	8.7		
No change		14	27.5		24	52.2		
Decrease/stop		33	64.7		18	39.1		
Insertive anal intercourse	58			49			7.40	.02
Increase		9	15.5		5	10.2		
No change		18	31.0		28	57.1		
Decrease/stop		31	53.4		16	32.7		
Active fellatio	60			52			2.34	.31
Increase		3	5.0		4	7.7		
No change		29	48.3		31	59.6		
Decrease/stop		28	46.7		17	32.7		
Passive fellatio	62			54			3.93	.14
Increase		8	12.9		7	13.0		
No change		34	54.8		38	70.4		
Decrease/stop		20	32.3		9	16.7		
Behaviors not considered to increase AIDS risk								
Looking at pornography	55			49			3.57	.17
Increase		23	41.8		12	24.5		
No change		30	54.5		34	69.4		
Decrease/stop		2	3.6		3	6.1		
Hugging and touching	61			54			2.76	.25
Increase		11	18.0		16	29.6		
No change		46	75.4		33	61.1		
Decrease/stop		4	6.6		5	9.3		
Masturbation	62			54			0.73	.69
Increase		29	46.8		21	38.9		
No change		31	50.0		31	57.4		
Decrease/stop		2	3.2		2	3.7		
Mutual masturbation	55			46			0.27	.87
Increase		22	40.0		20	43.5		
No change		31	56.4		25	54.3		
Decrease/stop		2	3.6		1	2.2		

variables (decrease or increase in AIDS risk behaviors) are shown in table 3. Overall, a little over one-third of the variance was accounted for in both groups for modeling both decrease and increase in possible AIDS risk behavior. However, the explanatory variables entering the model varied considerably between the two groups. For example, "can count on lover" entered at the first step and explained 24% of the variance in decreasing risk behavior for the physicians but entered at the fifth step and explained only an additional 5% of the variance for the student subjects. "Interest in sex" and "satisfaction with sex" before the AIDS epidemic entered the models for the students early but exhibited only slight explanatory power in one of the models for the physicians.

DISCUSSION

Both subject groups reported marked decreases in AIDS risk behaviors since the onset of the AIDS epidemic. Although the subjects in this report may not be representative even of politically active, openly gay male physicians or gay male university students generally (due to possible systematic group differences between study participants and nonparticipants), their responses provide further evidence that at least some groups of homosexual men are very knowledgeable about AIDS and its transmission and have dramatically altered their sexual behavior in a sophisticated way (16, 17, and unpublished work of K. Siegel et al.). Self-reports of changes in sexual behavior, particularly changes in sexual behaviors over long and unspecified periods of time, are susceptible to subject reporting bias (19).

Both groups accepted the prevailing scientific opinion that a high number of sexual partners, specific sexual acts, and exchange of bodily fluids are significant risk factors for AIDS transmission. The physician group had more personal knowledge than the student group had of individuals who had contracted AIDS or died from AIDS.

TABLE 3. Stepwise Multiple Regression Analysis[a] of Proportional Decrease and Increase in Possible AIDS Risk Behaviors in Homosexual Male Physicians and University Students

	Physicians			Students		
Step	Variable Entered	β	Cumulative R^2	Variable Entered	β	Cumulative R^2
Decrease in AIDS risk behavior						
Step 1	Can count on lover	−.78	.24	Number of trusted friends	−.35	.13
Step 2	Belief in vulnerability	.31	.31	Personal knowledge of AIDS	.28	.23
Step 3	Perceives self to be in high-risk group	.15	.35	Satisfaction with sex before AIDS	−.23	.28
Step 4	Lives with lover	.49	.37	Perceived level of gay community anxiety	.27	.33
Step 5	Perceives that gay men have changed sexual practices	.14	.38	Can count on lover	−.21	.38
Increase in AIDS risk behavior						
Step 1	Age	−.35	.15	Interest in sex before AIDS epidemic	.31	.06
Step 2	POMS total score	.25	.22	Number of friends	.73	.13
Step 3	Believes it is pointless to change sexual practices	.28	.28	Number of trusted friends	−.50	.25
Step 4	Perceived level of gay community anxiety	−.20	.32	Number of visits to physician in last 6 months	−.31	.31
Step 5	Interest in sex before AIDS	−.18	.35	Perceived level of gay community anxiety	−.21	.34

[a]The analysis was a forward stepwise multiple regression with no preselection.

Both groups felt that the AIDS epidemic had had a marked effect on the gay community and on gay men's sexual behavior. Both groups reported marked changes in their health-related, social, and gay community activities.

Change in health behavior has been related to the provision of clear, consistent, and ordered information to an individual (20), the individual's perception that he or she can alter the course of events through his or her own activity ("internal locus of control") (21), and the individual's beliefs regarding health (feeling of vulnerability to an adverse outcome and the beliefs that change is possible, that change will bring about a significantly positive outcome, and that the benefits of change outweigh its costs) (22, 23). Also, health behavior change may partially depend on the individual's "subjective norm," i.e., the degree of belief that one's peer group or significant others approve of one's behavior change (19).

Our findings are consistent with predictions from the "health belief model" (22, 23), as the subjects in our study who considered themselves members of a high-risk group and more vulnerable to AIDS were most likely to have decreased their AIDS risk behaviors. The lack of perceived control over the outcome ("It is pointless to change sexual habits") was correlated with an *increase* in AIDS risk behaviors in physicians. This finding is consistent with predictions from the literature on "locus of control."

The "subjective norm" model of health behavior change, as tested by our question concerning subject-perceived change in the sexual practices of gay men generally, was also supported by our findings.

Strong sexual interest before the AIDS epidemic, belief that one's sexual partner(s) is(are) safe, high levels of emotional distress, and knowing someone who has AIDS or has died from AIDS have previously been correlated with change in AIDS risk behaviors among homosexual men (17, and unpublished works of D.G. Ostrow et al. and J.G. Joseph et al.).

Sociodemographic factors, knowledge about AIDS, health beliefs, beliefs about control over outcome, mood state, sexual interest, and social support and social network characteristics may all be important contributing factors to change in AIDS risk behaviors among homosexual men. Thus, any model that attempts to explain sexual behavior in homosexual men must be multifactorial. A model that is powerful in accounting for behavior change in one group of homosexual men may not be as powerful in another group.

Likewise, interventions designed to bring about or sustain sexual behavior change in homosexual men need to be tailored for subgroups of the homosexual population. Our results suggest that programs designed to increase the sense of control over outcome might be most effective in older well-educated gay men, while appeals to peer group social norms may prove successful in effecting change in younger well-educated men.

Investigators have made significant progress toward understanding the pathophysiology of this deadly syn-

drome, and the media have focused public attention on AIDS and the many problems it poses. We are currently preparing a second survey of the same respondents that may reflect more profound or different changes in AIDS risk behaviors among these high-risk individuals. Meanwhile, as there is no cure, primary prevention continues to be the most effective deterrent of AIDS. As HIV infection and AIDS spread to the general population (24), many of the same assessment, model building, and intervention strategies currently being applied to the gay male population will need to be thoughtfully applied to high-risk heterosexual groups.

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Sexual Practices Among Patients With Borderline Personality Disorder

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The authors found that 12 (57%) of 21 consecutive male patients with borderline personality disorder who presented for psychiatric treatment at two distant geographic sites were homosexual. They then obtained the sexual histories of 80 patients who met standardized criteria for borderline disorder and found that 17 (21%) of these patients were homosexual, four (5%) were bisexual, and nine (11%) had diagnoses of paraphilias. Ten (53%) of the 19 men with borderline disorder were homosexual, compared with seven (11%) of the 61 women. Homosexuality was 10 times more common among the men and six times more common among the women with borderline personality disorder than in the general population or in a depressed control group.

(Am J Psychiatry 1987; 144:748–752)

Since Stern first used the term "borderline" in 1938 (1), borderline personality disorder has been defined in many ways, on both psychodynamic and descriptive grounds (2–4). Descriptions of this diagnostic group have typically included references to idiosyncrasies of sexual preference or practice. Borderline patients have been characterized as displaying a preoccupation with sex (5), confusion of sexual identity (5–7), pansexuality (5, 8), diverse sexual problems (2), sexual deviance (5–13), and polymorphous perverse sexuality (5, 10, 12, 14). In fact, *DSM-III* includes sexual impulsivity and disturbances of gender identity among the diagnostic criteria for borderline personality disorder. Yet, systematic empirical studies of the sexual behavior of patients with borderline personality disorder are lacking in the literature.

Received March 28; revised Oct. 20, 1986; accepted Dec. 8, 1986.
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Supported by Research Scientist Development Award MH-00540 to Dr. Zubenko, Research Grant MH-35392 to Dr. Soloff, and Clinical Research Center Grant MH-30915 from NIMH.
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In a pilot study of the rate of homosexuality in borderline disorder, one of us (G.S.Z.) found that 12 (57%) of 21 male patients with borderline personality disorder were predominantly or exclusively homosexual. In that study, sequential outpatients were evaluated at McLean Hospital in Belmont, Mass., or at Western Psychiatric Institute and Clinic in Pittsburgh, Pa. The diagnosis of borderline personality disorder was established by clinical interviews according to *DSM-III* criteria. To replicate and extend these findings, a second study was undertaken at the University of Pittsburgh using both male and female inpatients rigorously diagnosed according to Gunderson et al.'s semistructured Diagnostic Interview for Borderline Patients (15) to enhance the reliability of diagnosis. In addition, a broader range of sexual behaviors was addressed, including homosexuality, bisexuality, and paraphilias.

METHOD

Pilot Study

In the pilot study, sexual histories were elicited from 21 consecutive male patients who met *DSM-III* criteria for borderline personality disorder during initial evaluations at McLean Hospital in Belmont, Mass. (N=10) or the Diagnostic Evaluation Center at Western Psychiatric Institute and Clinic in Pittsburgh, Pa. (N=11). Sexual histories were also elicited from 20 consecutive male patients and 30 consecutive female patients under the age of 35 years who presented for initial evaluation at Western Psychiatric Institute and Clinic who met *DSM-III* criteria for major depression but not for borderline personality disorder.

In Belmont, patients were scheduled for initial evaluations in order of presentation and according to the clinician's caseload. All patients who were evaluated in Pittsburgh were seen in the order in which they presented. Patients were unaware of the identity of the clinician who would perform their evaluation when they contacted the evaluation services at either institution.

All 71 diagnostic evaluations were conducted by the same clinician (G.S.Z.) and lasted approximately 50

minutes. The *DSM-III* diagnoses of borderline personality disorder and major depression as well as the determination of homosexuality were confirmed by independent clinicians who were blind to the hypothesis being tested. Patients were considered homosexual if they were entirely or almost entirely homosexual in their overt activities and reactions to individuals of the same or opposite sex, as determined by their scoring at least five out of a possible six points on the homosexual-heterosexual rating scale of Kinsey et al. (16).

Second Study

The study population for the second study consisted of 80 consecutive inpatients who were recruited to participate in a study of pharmacology of borderline disorders (17). Patients were referred for evaluation if their primary clinician made a presumptive clinical diagnosis of borderline or schizotypal personality disorder or both. Following a thorough psychiatric and medical evaluation, informed consent was obtained and the Diagnostic Interview for Borderline Patients (15) was administered. This instrument collects information from five different areas: social adaptation, impulse/action patterns, affects, psychosis, and interpersonal relations. Raw scores determining the number and severity of symptoms within each area are converted to scaled subscores ranging from 0 to 2. The five resulting scaled subscores are combined to produce a total scaled subscore ranging from 0 to 10. A total scaled score of 7 or more was required for a diagnosis of borderline personality disorder, as recommended by Kolb and Gunderson (18).

DSM-III subtype diagnoses of borderline or schizotypal personality disorder or both were made on the basis of direct patient interviews. The *DSM-III* diagnosis of schizotypal personality disorder in patients screened by the Diagnostic Interview for Borderline Patients identifies individuals with borderline disorder who have prominent schizotypal symptoms, such as referential thinking, paranoid ideation, and derealization, in the context of otherwise typical borderline affects, impulsiveness, and interpersonal relatedness.

The exclusion criteria of chronicity, medical disorder, and organicity were adopted from Gunderson et al. (19). Patients warranting current Research Diagnostic Criteria (RDC) (20) diagnoses of schizophrenia, schizoaffective disorder, manic disorder, bipolar disorder with mania, or hypomania by clinical evaluation or interview according to the Schedule for Affective Disorders and Schizophrenia (SADS) (21) or a valid past diagnosis by history, chart review, or interview on the lifetime version of the SADS (SADS-L) (22) were excluded from the study. Patients meeting RDC (by clinical history or SADS) for a current diagnosis of major depression were included, since major depression has been reported in 14%–15% of borderline patients depending on sample, setting, and study methods (23, 24).

Sexual history was obtained by review of the impulse/action patterns and interpersonal relations sections of the Diagnostic Interview for Borderline Patients, from the review of patients' charts, and from clinical interviews. Patients were considered homosexual at the time of evaluation if they met the criteria of Kinsey et al. (16) described for the pilot study. Patients who had a history of ambivalence concerning the preferred sex of their sexual partner and who had engaged in sexual activity with individuals of both sexes were considered bisexual. Paraphilias included the *DSM-III* diagnoses of fetishism, transvestism, zoophilia, pedophilia, exhibitionism, voyeurism, sexual masochism, sexual sadism, and atypical paraphilias.

Comparisons of categorical variables between groups were made by using the chi-square statistic. Comparisons of continuous variables between groups were made by using two-tailed t tests.

RESULTS

Pilot Study

Twelve (57%) of the 21 male patients who met *DSM-III* criteria for borderline personality disorder in the pilot study were predominantly or exclusively homosexual. The rates of homosexuality among the Belmont and Pittsburgh samples were similar: six (60%) of the 10 Belmont patients and six (55%) of the 11 Pittsburgh patients. None of the 12 homosexual patients described his homosexuality as ego dystonic. All 12 still met *DSM-III* criteria for borderline personality disorder after gender identity disturbance had been excluded from the diagnostic criteria.

In the male population of the United States, the accumulative rate of homosexuality increases during the first and second decades of life, plateaus in the third decade, and declines gradually thereafter (16). The mean±SD ages of the homosexual (23.7±2.7 years) and heterosexual (23.3±3.3 years) Belmont patients were similar to those of the homosexual (25.3±4.4 years) and heterosexual (24.6±4.8 years) Pittsburgh patients. Moreover, the mean ages of the homosexual and heterosexual patients were similar to each other at both locations and in the combined sample. The mean±SD age of all 10 Belmont patients was 23.5±2.8 years; for the 11 Pittsburgh patients it was 25.0±4.4 years. The mean±SD age of all 12 homosexual patients was 24.5±3.6 years; for the nine heterosexual patients it was 24.0±4.0 years. The mean ±SD age of all 21 patients was 24.3±3.7 years. Twenty of the 21 patients were Caucasian, and one was black.

The sexual histories of control groups of 20 consecutive male patients and 30 consecutive female patients between the ages of 18 and 37 years who presented for initial evaluation at Pittsburgh and who met *DSM-III* criteria for major depression but not for borderline personality disorder were also elicited. The 18–37-year

age range was chosen to make the control groups similar in age to the borderline sample. The resulting groups of depressed men and women had mean±SD ages of 25.1±4.2 years and 26.2±5.2 years, respectively, similar to the mean age of the 21 borderline patients. Eighteen of the 20 depressed men and 27 of the 30 depressed women were Caucasian; the remainder were black. Only one of the depressed men and none of the depressed women met our criteria for homosexuality. Unlike the men with borderline personality disorder, the depressed man described his homosexuality as ego dystonic. Significantly more of the men with borderline personality disorder (12 of 21) than of either depressed men (χ^2=12.86, df=1, p=.0006) or depressed women (χ^2=22.42, df=1, p< .0001) of similar mean age were homosexual.

Second Study

Of 80 sequential patients who met Diagnostic Interview for Borderline Patients criteria for borderline personality disorder, 19 were men and 61 were women. This is in agreement with studies showing that the number of women with this diagnosis is consistently greater than the number of men with this diagnosis (18, 23, 25–28). The mean±SD ages of the men and women in this study (25.3±6.3 years and 24.7±5.4 years, respectively) were similar to one another and to the mean ages of the 50 depressed patients in the pilot study. All but four of the 80 subjects met *DSM-III* criteria for borderline personality disorder as well as the Diagnostic Interview for Borderline Patients criteria.

Nine (47%) of the 19 men with borderline personality disorder were heterosexual, compared with 54 (89%) of the 61 women (χ^2=14.66, df=1, p=.0003). Ten (53%) of the men were homosexual, compared with only seven (11%) of the women (χ^2=14.66, df=1, p=.0003). One (5%) of the men and three (5%) of the women were bisexual. Three (16%) of the men and six (10%) of the women had diagnoses of paraphilias. Specific paraphilias among the men included sexual sadism, sexual masochism, and an atypical paraphilia. Among women, paraphilias included zoophilia, pedophilia, sexual masochism, and atypical paraphilias. Twenty-one (26%) of the 80 individuals in the study population were either homosexual or bisexual or had a diagnosis of paraphilia or any combination of these. Of these 21 patients, 13 (62%) satisfied criteria for two of these items and one (5%) satisfied criteria for all three.

To address the issue of whether homosexuality affected the severity of borderline personality disorder in our study population, we corrected the total raw Diagnostic Interview for Borderline Patients scores by deleting the contribution of the item on sexual deviance (pattern of promiscuity, homosexuality, or repetitive sexually deviant practices) and used the resulting corrected total raw score as an indication of number and severity of symptoms. As shown in table 1, the presence of homosexuality in patients of either sex was not associated with a significantly higher number or greater severity of borderline symptoms, as reflected by the corrected total raw Diagnostic Interview for Borderline Patients score.

TABLE 1. Relationship of Sexual Preference to Impulse/Action Patterns Score and Total Corrected Raw Score[a] on the Diagnostic Interview for Borderline Patients of 80 Patients With Borderline Personality Disorder

Patients' Sex and Sexual Preference	Impulse/Action Patterns Score		Total Raw Score	
	Mean	SD	Mean	SD
Men (N=19)	4.7	2.3	26.5	7.2
Homosexual (N=10)	5.6	2.5	29.3	9.2
Heterosexual (N=9)	4.0	1.9	24.0	3.8
Women (N=61)	5.5	2.6	27.6	5.0
Homosexual (N=7)	6.7	3.6	28.0	4.4
Heterosexual (N=54)	5.3	2.5	27.6	5.1

[a]Exclusive of question regarding sexual deviance.

TABLE 2. Relationship of Sexual Preference and Diagnoses of Paraphilias to *DSM-III* Diagnosis of Schizotypal Personality Disorder in 80 Patients With Borderline Personality Disorder

Patients' Sexual Preference or Diagnoses of Paraphilias	Schizotypal Personality Disorder Present (N=50)		Schizotypal Personality Disorder Absent (N=30)	
	N	%	N	%
Heterosexual	41	82	22	73
Homosexual	9	18	8	27
Bisexual	2	4	2	7
Paraphilias	5	10	4	13

We performed an analogous analysis using only the corrected raw scores on the impulse/action patterns scale of the Diagnostic Interview for Borderline Patients, since the question regarding sexual deviance resides within this subsection. Homosexuality was not associated with a significantly higher score on the corrected raw impulse/action patterns scale (table 1).

The relationship of sexual preference and diagnoses of paraphilias to the presence or absence of a *DSM-III* diagnosis of schizotypal personality disorder is shown in table 2. The presence of schizotypal personality disorder was not associated with a statistically significant change in the rates of homosexuality, bisexuality, or paraphilias.

The inclusion or exclusion of the single criterion of sexual deviance from the Diagnostic Interview for Borderline Patients had little impact on the composition of the borderline sample. After the deletion of this criterion from the raw impulse/action patterns score and subsequent recalculations of the resulting total scaled score, only five of the 80 borderline patients failed to meet the cutoff score of 7. The exclusion of these five patients had no significant effect on the rates of homosexuality, bisexuality, or paraphilias in the borderline sample. Nine (53%) of the 17 remaining men, compared with six (10%) of the 58 remaining women, were homosexual (χ^2=14.91, df=1, p=

.0003). One (6%) of the men and two (3%) of the women were bisexual, while three (18%) of the men and six (10%) of the women had diagnoses of paraphilias. Moreover, since the same diagnostic criteria were applied to both men and women, the inclusion of sexual deviance among the diagnostic criteria did not account for the higher rate of homosexuality among men in comparison with women.

DISCUSSION

In the prospective pilot study, we found that 57% of male outpatients who met *DSM-III* criteria for borderline personality disorder were predominantly or exclusively homosexual. Since the association was equally robust within outpatient psychiatric populations at Belmont, Mass., and Pittsburgh, Pa., this finding is unlikely to be the result of an idiosyncrasy of geographic location or referral source. The second study, which used a standardized diagnostic interview to diagnose borderline personality disorder, confirmed and extended this association in an inpatient setting. Since the patient population of the latter study did not overlap with that of the pilot study, the association of homosexuality with borderline personality disorder in male patients was observed in a total sample of 40 men with borderline personality disorder.

The rate of homosexuality among male inpatients who met Diagnostic Interview for Borderline Patients criteria for borderline disorder was 53%, similar to that found in the pilot outpatient study and significantly higher than the corresponding figure for women with borderline disorder (11%). Although the rate of homosexuality among men and women in the general population is a function of age (16), the mean ages of the male and female groups of borderline patients in this study were closely matched. Therefore, potential differences in age did not contribute to the gender-related difference in the observed rate of homosexuality among borderline patients.

To compare our results with those obtained for the general U.S. population, we adopted a definition of homosexuality from the studies of Kinsey et al. (16). Their data revealed a 5.2% rate of homosexuality among 25-year-old men (N=1,835), irrespective of educational history. Estimates of the rate of male homosexuality in the U.S. population by Gebhard (29) are somewhat lower (approximately 4%). The rate of homosexuality that we observed in our sample of male patients who met Diagnostic Interview for Borderline Patients criteria for borderline disorder was at least 10 times higher than the estimate of Kinsey et al. (16) ($\chi^2=79.26$, df=1, $p<.0001$). In contrast, we found that only one out of 20 sequential male outpatients who met *DSM-III* criteria for major depression also met our criteria for homosexuality, a rate significantly lower than that observed for our male borderline patients of similar age (10 of 19) ($\chi^2=11.47$, df=1, $p=.001$) but not significantly different from the rate of male homosexuality in the general population reported by Kinsey et al. (16).

Kinsey et al. (30) also reported a 1.8% rate of homosexuality among 25-year-old women (N=2,824) in the general population, regardless of educational or marital status. Gebhard's estimate (29), 1%–2%, was similar to that of Kinsey et al. (30). We observed a rate of homosexuality in our sample of female borderline patients that was approximately six times higher than that estimated by Kinsey et al. (30) ($\chi^2=20.34$, df=1, $p<.0001$). By comparison, none of 30 consecutive female outpatients who met *DSM-III* criteria for major depression also met our criteria for homosexuality. This rate was significantly lower than that observed for the female borderline patients of similar age ($\chi^2=3.73$, df=1, $p=.05$) but not significantly different from the rate of female homosexuality in the general population reported by Kinsey et al. (30). Therefore, the higher rate of homosexuality that we observed among borderline patients in the current study does not appear to be a nonspecific concomitant of psychiatric illness or to reflect an unusually high rate of homosexuality in the entire patient population at our institution. Although none of the homosexual borderline patients described their sexual preference as ego dystonic, it is possible that the coexistence of homosexuality and borderline personality disorder increases the likelihood of presentation for psychiatric evaluation. In this case, the observed rate of homosexuality among borderline patients who presented for evaluation might be an overestimate of the association of these conditions in the general population.

Although data on the population rates of bisexuality and paraphilias are lacking, virtually all reported cases of paraphilias have been in males according to *DSM-III*. In contrast, the rates of bisexuality and paraphilias in patients with borderline personality disorder were similar for men and women in our sample. It is our impression that the rates of bisexuality and paraphilias in the total borderline sample, 5% and 11%, were high in comparison with the rates in the general population.

Empirical studies of the association of homosexuality with psychiatric disorders are scant, and, to our knowledge, no empirical studies of the association of bisexuality or paraphilias with another psychiatric disorder have been reported. Using a broader definition of homosexuality than that used in our study, Taylor and Abrams (31) found a 16% rate of homosexuality for a group of 50 manic patients with a mean age of 41 years. It is difficult to compare our results with theirs, especially since our use of a more restrictive definition of homosexuality and a younger patient population would be expected to produce opposing effects on the observed rate (16, 30).

Several lines of evidence suggest that the observed higher rate of homosexuality among men with borderline personality disorder, which predominantly affects women (2), may be analogous to the reported increased rate of homosexuality among women with sociopathy, which predominantly affects men (32, 33).

Although it is possible that the latter finding reflects prison experience rather than the presence of sociopathy per se, Guze et al. (33) did not find a higher rate of homosexuality in a similar group of sociopathic men. Kernberg (34) has suggested a relationship between borderline, histrionic, and antisocial personality disorders. Moreover, Pope et al. (35) failed to find evidence to validate borderline personality disorder as separate from histrionic personality disorder or antisocial personality disorder using phenomenology (symptoms), family history, treatment response, and long-term follow-up as validating indexes.

In summary, these empirical data support the inclusion of homosexuality, bisexuality, and paraphilias in diagnostic formulations of borderline personality disorder. However, since 75 of the 80 patients who met the full Diagnostic Interview for Borderline Patients criteria for borderline personality disorder still satisfied these criteria after the exclusion of sexual deviance from consideration, the diagnosis of borderline personality disorder does not rely exclusively on these symptoms.

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Eye Versus Skin Phototherapy of Seasonal Affective Disorder

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In winter, depressed patients with seasonal affective disorder respond to treatment with bright artificial light (phototherapy). The authors found that the antidepressant effects of phototherapy were much greater for 10 patients when light was applied to the eyes than when it was applied to the skin, suggesting that its effects may be mediated by the eyes. The identification of a probable anatomical route of entry is clinically relevant and an important clue for further investigations of the mechanism of phototherapy. However, patients' expectations nearly always predicted the outcome, leaving open the possibility that expectations were responsible for their responses.

(Am J Psychiatry 1987; 144:753–757)

Seasonal affective disorder is characterized by recurring cycles of fall-winter depression and spring-summer hypomania or euthymia. Depressive symptoms often include hypersomnia, anergia, fatigue, carbohydrate craving, and weight gain. The syndrome occurs predominantly in women and usually begins early in adulthood (1). In winter, most depressed patients with seasonal affective disorder respond within 2–3 days to daily treatments of 2–6 hours of bright artificial light and relapse 2–3 days after light is withdrawn (1–9).

The idea of using light to treat winter depression was derived from animal studies showing that changes in length of day (photoperiod) trigger seasonal changes in behavior and physiology in many species (10, 11). This effect of light on seasonal rhythms in animals is mediated by neural pathways leading from the eye to the hypothalamus and thence to the pineal gland. Light modifies the pattern of pineal melatonin secretion, which acts as a chemical signal causing target sites in the organism to respond in a seasonally appropriate manner (12). The discovery that bright artificial light is capable of suppressing human nocturnal melatonin secretion suggested that the retino-hypothalamic-pineal axis is functionally intact in humans and that it might mediate the effects of seasons on mood in patients with seasonal affective disorder. The early studies of phototherapy were inspired by this finding. However, the results of a series of studies have led us to question whether this eye-mediated mechanism, resulting in modification of the pattern of melatonin secretion, is a likely explanation for the mode of action of phototherapy.

The strongest evidence against this model was our finding that light administered during daylight hours is an effective treatment for seasonal affective disorder even though it does not extend the apparent length of the day and does not alter the pattern of nocturnal melatonin secretion (8). Other evidence is more equivocal. Administration of melatonin does not clearly reverse the antidepressant effects of phototherapy, although it does induce some depressive symptoms, such as fatigue, increased sleep, overeating, and carbohydrate craving (13). Administration of atenolol, a β-adrenergic antagonist drug that suppresses melatonin secretion and thus mimics the effect of light on the pineal gland, was not superior to placebo in the treatment of seasonal affective disorder; nevertheless, a few individuals clearly seemed to respond to the drug (13). These mixed results, which cast doubt on the hypothesis that melatonin is of central importance in the antidepressant effects of light in most cases of seasonal affective disorder, led us to question our basic assumption that the antidepressant effects of light are mediated by the eye. Could they perhaps be mediated instead through the skin, as is the case with vitamin D synthesis (14), the lowering of serum bilirubin in neonatal jaundice (15), and certain immunologic reactions (16)? To address this question we conducted a crossover study in which we compared the antidepressant effects of eye exposure and skin exposure to light in depressed patients with seasonal affective disorder.

Excluding the placebo effect has been a major methodological problem in the evaluation of the efficacy of phototherapy. The usual techniques of double-blind studies cannot easily be applied when light is used as a treatment. It has been difficult to find a plausible control treatment for this purpose; different intensities, spectra, durations, and timing of light administration have been tried (1,3,6–9). Since the effects of sunlight on both skin and eyes have powerful emotional associations for people, it seemed to us that a comparison between skin and eye exposure to the same light source

Received April 28, 1986; revised Oct. 14, 1986; accepted Dec. 5, 1986. From the Clinical Psychobiology Branch, National Institute of Mental Health. Address reprint requests to Dr. Wehr, NIMH, Room 4S-239, Bldg. 10, 9000 Rockville Pike, Bethesda, MD 20892.

would provide a good opportunity to evaluate the possible relationship between initial expectations and treatment outcome.

METHOD

Patients with seasonal affective disorder were referred by psychiatrists familiar with our program or were recruited by means of a newspaper article describing our interest in the syndrome. Criteria for entry into the study were 1) diagnosis of major depressive disorder according to Research Diagnostic Criteria (RDC) (17), 2) diagnosis of seasonal affective disorder according to the criteria of Rosenthal et al. (1), 3) Hamilton Rating Scale for Depression (18) score of 15 or more, and 4) willingness and ability to undergo the rigorous conditions of the experiment. Patients who had participated in phototherapy studies during previous winters were not excluded, but they accounted for only three of the 10 patients who completed the study.

In the winter, during two different 7-day periods, depressed patients with seasonal affective disorder were exposed to two different 4-hour light treatments each evening from approximately 6:30 to 10:30 p.m. on a research ward at the National Institute of Mental Health (NIMH). During one 7-day period, the patients' skin (face, neck, arms, and legs) was exposed to the light while their eyes were shielded with goggles fitted with neutral density filters. Light admitted by the filters was just sufficient to permit television viewing. During the other 7-day period, patients' eyes were exposed to the light while their skin was completely shielded with a mask and a cloth barrier. During this condition patients were instructed not to stare at the lights but to glance at them every minute or so. In both conditions patients were encouraged to watch television or listen to music to relieve the tedium of the experiment.

The two treatments were administered in a balanced randomization crossover design with at least 7 days between treatment periods to allow for relapse before the second treatment. Patients were required to have a Hamilton depression scale score of 15 or more before beginning the second treatment. Light for the treatments consisted of 2500 lux of full-spectrum light (Vitalite) emitted from a rectangular metal fixture containing eight fluorescent tubes behind a plastic diffusing screen. This light source produces a small amount of ultraviolet light, most of which is transmitted through the screen; its precise spectral characteristics have been described in detail elsewhere (19). Patients sat 3 feet away from the light, which was at eye level. They were instructed not to sleep during the treatments. All patients gave informed consent before participating in the study.

Great care was taken with regard to the information that was given to the patients before and during the experiment. At the beginning of the study, patients were given a document stating that "people who regularly become depressed in the fall and winter experience an improvement in their symptoms when they are treated with light." It also stated that the "manner in which light exerts its beneficial effects is unknown" and that "a series of studies at the NIMH have cast doubt on our original notions about the possible biological mechanisms of light therapy." The document then provided logistical details about the study but no information about the comparison that was to be made between eye and skin treatments.

At the beginning of each treatment a research assistant gave each patient another written document that described that particular treatment and made explicit our intention to expose their eyes but not their skin, or vice versa, to the light. The alternative treatment was not mentioned or described at that time. Next, the research assistant briefly placed the patient in the treatment condition and asked him or her to fill out a form that was designed to evaluate expectations of the treatment by means of a scale in which 0 indicated an expectation of no improvement or no worsening, 4 indicated an expectation of very much improvement, and −4 indicated an expectation of very much worsening.

Finally, before beginning the first treatment session, patients were given another written document that encouraged them to try to disregard their expectations and simply report how they actually felt at the end of the treatment. Patients, research assistants, nurses, and physicians were asked not to discuss the treatments.

Two psychiatrists blind to the treatment conditions (T.A.W. and D.A.S.) evaluated the patients' clinical state before and after each treatment and after withdrawal of treatment (7 days after the last day of treatment) using the Hamilton depression scale. Ratings obtained before and after treatment were subjected to an analysis of variance with one grouping factor (sequence of treatment administration) and two repeated measures (before versus after treatment and skin phototherapy versus eye phototherapy). Hamilton change scores were calculated by subtracting scores obtained during treatment from scores obtained before treatment.

RESULTS

Ten patients (nine women and one man) completed both phases of the experiment. Four patients were assigned to the eye treatment first and six to the skin treatment first. Two other patients dropped out of the study during the first condition: one discontinued the eye treatment because of eye irritation and the other discontinued the skin treatment because it seemed to have no therapeutic effect. A third patient responded to the first condition (eye treatment), but the physicians who were blind to treatment conditions excluded her from the study during the second condition (skin treatment) because a flu-like illness made it difficult to evaluate her response to treatment. A fourth patient

TABLE 1. Hamilton Depression Scores of 10 Patients With Seasonal Affective Disorder Treated With Eye and Skin Phototherapy

Patient	Treatment Given First	Score on Hamilton Rating Scale for Depression[a]					
		Eye Phototherapy			Skin Phototherapy		
		Baseline	During Treatment	During Withdrawal	Baseline	During Treatment	During Withdrawal
1	Eye	30	5	21	21	26	—
2	Eye	17	16	15	15	9	11
3	Eye	35	22	31	31	20	26
4	Eye	20	7	14	24	17	—
5	Skin	32	8	25	27	33	32
6	Skin	35	3	26	34	30	35
7	Skin	15	0	22	17	21	15
8	Skin	27	25	13	19	0	27
9	Skin	19	5	16	21	24	19
10	Skin	26	12	22	25	23	26
Mean		25.6	10.3	20.5	23.4	20.3	23.9
SD		7.5	8.3	6.1	6.0	9.8	7.3

[a]Significant effect for Treatment by Condition ($F=5.97$, $df=1,9$, $p<.05$).

TABLE 2. Accuracy of Eight Patients' Predictions of Their Response to Eye Versus Skin Phototherapy

Patient	Prediction of Magnitude of Improvement[a]		Hamilton Change Score[b]		Accuracy
	Eye Phototherapy	Skin Phototherapy	Eye Phototherapy	Skin Phototherapy	
1	2	1	25	−5	Correct
2	1	3	1	6	Correct
3	3	3	13	11	Correct
5	3	−2	24	−6	Correct
7	0	0	15	−4	Incorrect
8	3	4	2	19	Correct
9	4	3	14	−3	Correct
10	3	−1	14	−3	Correct
Mean	2.2	1.2	15.3[c]	2.6	
SD	1.3	2.1	9.7	8.2	

[a]Self-rating of expectation of treatment: −4=very much worsening, 0=no change, and 4=very much improvement.
[b]Positive numbers indicate lower Hamilton scores and improvement in depression.
[c]Significantly more improvement ($t=2.443$, $df=9$, $p<.05$).

was unable to complete the study because she failed to relapse after she responded to the first condition (eye treatment).

The eye treatment was superior to the skin treatment. Analysis of variance showed a statistically significant Treatment by Condition interaction (table 1). For the group, post hoc analysis with paired t tests showed that changes in Hamilton depression scale scores between baseline and treatment were statistically significant for the eye condition only ($t=4.996$, $df=9$, $p<.001$) and that differences between responses to the two conditions were statistically significant ($t=2.443$, $df=9$, $p<.05$).

According to their Hamilton depression scale scores, seven patients clearly responded to the eye treatment and not to the skin treatment (patients 1, 4, 5, 6, 7, 9, and 10). One patient (patient 8) clearly responded to the skin treatment and not to the eye treatment. One patient (patient 3) responded to both treatments. One patient (patient 2) responded little to either treatment but responded more to the skin treatment.

Ratings of expectations of both treatment conditions were available for eight patients (table 2). In general, patients' expectations were positive. Although there were no statistically significant differences between expectations of the two procedures (Wilcoxon sign-rank test), patients tended to favor the eye condition. Five patients expected some benefit from both conditions. Two expected some benefit from the eye condition but worsening from the skin condition. One expected no benefit from either condition. If patients' expectations are categorized as favoring the eye condition (patients 1, 5, 9, and 10), favoring the skin condition (patients 2 and 8), or equal for the two conditions (patients 3 and 7), their expectations correctly predicted the outcome in seven of eight cases.

DISCUSSION

In this study exposure of the eyes to light was associated with an antidepressant effect that was superior to that of exposure of the skin to light. Among the 10 patients there was only one whose responses were clearly incompatible with this conclusion (patient 8). As it turned out, two additional patients who completed the first condition but were unable to complete the second had also responded to the eye treatment.

The magnitudes of changes in Hamilton depression scale ratings with eye and skin treatments closely resemble those observed in previous studies where an active form of phototherapy was compared with an inactive one (1, 3, 4). Thus, whatever the nature of the response to phototherapy as administered in our previous studies, it seems to be much more effective when applied to the eyes than when applied to the skin. Perhaps it is worth noting that the identification of a specific neural structure as the principal or most effective site of action of a particular treatment modality is a novel development in psychiatry. In the light of these experimental results it seems logical to focus the search for possible biological mechanisms of phototherapy on processes in the retina or in structures that receive retinal projections, such as the hypothalamus. At the same time, the possibility of an independent, skin-mediated route cannot be excluded at this time.

We were aware that the present experiment would provide a valuable opportunity to determine whether there was any relationship between patients' expectations and their responses to phototherapy. First, we were uncertain which type of treatment, eye or skin, would be effective. Second, it seemed likely that both types of treatment would be credible interventions from the patients' point of view. They could observe that precisely identical light intensities, durations, and timing were used for each type of treatment. The materials and devices used to ensure that skin and eyes were selectively exposed to the light heightened the dramatic impact of each intervention, albeit in different ways. Although the possible role of skin had not been emphasized in publicity about phototherapy for seasonal affective disorder, the exposure of skin to sunlight has many positive associations in our culture, as evidenced by the growing popularity of tanning salons, and we believed that these associations would lend credibility to the skin treatment condition.

As it turned out, patients' expectations of the two types of phototherapy were highly predictive of their responses. This finding underscores the importance of inquiring about patients' expectations before administering phototherapy. It does not prove that patients' expectations are responsible for their responses but leaves open this possibility. Patients usually have expectations about the possible effects of treatments, and these expectations may be correct whatever the nature of the response (we all expect antibiotics to work, but this does not imply that our expectations are responsible for their efficacy). Problems involving the influence of patients' expectations and the credibility of sham interventions are not unique to this particular type of antidepressant treatment. For instance, there is evidence that patients involved in studies of the efficacy of antidepressant medications are not necessarily blind to differences between placebo and active treatments (20), and, until 1978 (21, 22), there were no controlled studies of the efficacy of ECT that employed sham treatments. Placebo effects and spontaneous remissions are major factors in studies of all types of treatment of depression. Clearly, the role of patients' expectations in their responses to phototherapy deserves further study. The development of methods whereby differences between active and inactive treatments can be disguised, however, will require considerable ingenuity.

On the basis of this and previous experiments we now know some of the properties of phototherapy that are essential for its therapeutic effect and some that are not. Intensity (1–3) and duration (9) appear to be important factors. As we have seen, light applied to the eyes is much more effective than light applied to the skin. This finding strongly suggests that exposure of the eyes is a necessary condition for the response in most patients, but it does not rule out the possibilities that light with spectral characteristics different from the ones used in this study might have antidepressant effects when applied to the skin or that a subgroup of patients might respond when their skin is exposed to the light used in this study. Time of day of treatments is not a critical factor (8), although it may influence the magnitude of patients' responses (6, 9). With regard to this variable the present study corroborates the finding of James et al. (4) that phototherapy administered only in the evening is effective. Interruption of sleep is not a necessary condition (3). The wavelengths of light that are necessary for the antidepressant effect of phototherapy are as yet unknown.

Phototherapy is an effective treatment for seasonal affective disorder, and it is likely that it will continue to be used. In the meantime, research into the possible role of patients' expectations in their responses and investigation of possible biological mechanisms of phototherapy must proceed in parallel.

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Follow-Up of Pathological Gamblers After Treatment

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Pathological gamblers entering a comprehensive treatment program were thoroughly assessed before treatment and 6 months after completion of treatment. The reports of gamblers and collateral informants were highly consistent. Follow-up interviews were conducted with 57 of the 66 patients entering treatment. Total abstinence was reported by 56% (N=32) of the patients located for follow-up, and significant improvement on a wide range of measures was documented. The authors feel that the results demonstrate that pathological gambling is a treatable mental disorder.

(Am J Psychiatry 1987; 144:757–761)

More than 10 years ago it was estimated that pathological gambling directly affected 1.1 million Americans (1). Recent estimates have indicated further growth of the problem (2). Certainly the opportunities for recreational gambling and the publicity about gambling have increased as, for example, casino gambling has become more prevalent, state lotteries have experienced tremendous growth, and a volatile stock market provides gambling options to the more upwardly mobile. Pathological gambling is, furthermore, a complex mental health problem often seen in conjunction with other syndromes, including depression (3, 4) and substance abuse (5).

Despite the prevalence of pathological gambling, there have been very few published reports on the treatment of the disorder. Reports on individual psychotherapy with pathological gamblers, while important, generally provide little in terms of outcome results (e.g., 6–8). The same can be said of reports of group therapy with gamblers (9). Bergler (10) claimed a 75% success rate among approximately 60 gamblers he treated in his practice, but this outcome estimate was based on his clinical assessment and recollection.

There have been a limited number of studies on the efficacy of behavioral approaches with pathological gamblers. Barker and Miller (11) reported three cases of compulsive gambling successfully treated in a hospital with electric shock. Other small-sample studies have also documented positive effects through aversion therapy (12–15). A more recent report on a series of 20 behavior therapy patients that compared the results of aversion therapy with imaginal desensitization found that at 1–year follow-up, none of the aversion therapy

Received May 29, 1986; revised Oct. 7, 1986; accepted Nov. 20, 1986. From the Cleveland VA Medical Center. Address reprint requests to Dr. McCormick, Brecksville Unit, Cleveland VA Medical Center, 10000 Brecksville Rd., Brecksville, OH 44141.

patients had abstained and seven (70%) reported their gambling as unchanged, while two (20%) of the desensitization patients reported no gambling (16). Greenberg and Rankin (17) reported on 26 compulsive gamblers who came to a hospital clinic over a period of 8 years. A variety of behavioral methods resulted in some degree of controlled gambling in only five of the patients.

Structured inpatient treatment programs for pathological gamblers, often modeled after programs for alcoholics and other substance abusers, have begun to appear in this country. An early report of a mail follow-up study on a long-established program reported favorable outcomes for 55% of the respondents (18). However, only 48% of the former patients responded to the follow-up inquiry, and the measure used was a simple questionnaire.

This article presents the results of a more comprehensive, prospective follow-up study on a cohort of patients completing the same structured inpatient program for pathological gamblers. Gambling behavior and general psychiatric functioning were evaluated. Although studies of substance abusers support the veridicality of patient self-reports, structured interviews were conducted (whenever possible) with the family member or friend having the most contact with the gambler in order to obtain collateral verification of reported gambling behavior.

METHOD

Subjects

Subjects consisted of 66 patients consecutively admitted to the gambling treatment program at the Cleveland Veterans Administration Medical Center. The program, which has been described in detail elsewhere (18), consists of a 28-day inpatient stay in a highly structured program housed within an alcohol treatment unit. Patients are referred to the program from contacts, primarily with Gamblers Anonymous groups, throughout the United States. All patients had serious gambling problems, met *DSM-III* criteria for pathological gambling, and generally had tried and failed outpatient treatment for their problem. Patients ranged in age from 24 to 74 years (mean=43 years). All were male veterans.

Assessment Instruments

The Psychiatric Status Schedule (19) is a structured interview that has been shown to be sensitive to changes in psychiatric status over time. It yields scores on symptom variables as well as summary scores on four symptom constellations and a summary index of functioning in important life roles.

In the Time Line Follow Back Month portion of the assessment, the patient is assisted in reconstructing the amount of gambling behavior for each day during the past month. The procedure is a modification of a follow-up technique used with substance abusers (20). The month is reviewed in detail and significant events that occurred during the month are used as anchors in time; each day is assessed and rated as having involved heavy, moderate, light, or no gambling. Both the number of days in which any gambling occurred and a weighted score for the month (3=heavy, 2=moderate, 1=light, 0=abstinent) are recorded.

The Gambling Behavior Survey collects information on a variety of dimensions of gambling behavior during the past month and in some cases during the past 6 months. Included are measures of the number of days abstinent, the amount of money gambled, the amount of time spent gambling, the number of days missed from work due to gambling, the number of outpatient and Gamblers Anonymous sessions attended, and illegal behavior and institutionalization.

Procedure

All subjects received their initial assessment on the Psychiatric Status Schedule, Gambling Behavior Survey, and Time Line Follow Back Month when they were interviewed for admission to the program. At the same time they were thoroughly questioned regarding their interpersonal relationships, and the person with whom they had the most regular contact was identified. An attempt was then made to contact and interview the collateral informant over the telephone. Collateral informants were evaluated with a modification of the Gambling Behavior Survey, in which they were asked questions regarding the gambling of the identified patient. The sample month used for these initial measurements was the 30-day period before the date of the patient's initial contact with the program. This time period, rather than the month before admission, was sampled so as to minimize any influence on gambling behavior or psychiatric status that anticipation of treatment might have had. Extensive and detailed tracking data (e.g., telephone numbers, addresses, people who might know the patient's whereabouts) were also collected from each subject at the time of the initial interview in order to facilitate later follow-up.

Data were collected by three interviewers who had worked in the gambling treatment program and were very familiar with pathological gambling. One had a master's degree in clinical psychology, one was working toward a master's degree in clinical psychology, and one was a baccalaureate student in psychology. During their training, interviews were conducted by one rater and observed and rated by another. Differences were minor and were discussed until consensus was reached on rating procedures, but detailed reliability measures were not computed.

In order to keep track of follow-up subjects, they were contacted by telephone 3 months after their discharge from the program. Six months after discharge from the program, an attempt was made to

TABLE 1. Descriptive Data for Pathological Gamblers Who Were and Were Not Followed Up After Treatment

Measure[a]	Subjects Followed Up (N=57) N	%	Subjects Not Followed Up (N=9) N	%	χ^2 (Yates' correction)	df	p
Marital status							
Married	30	53	3	33			
Divorced or separated	16	28	3	33	1.380	2	<.50
Single	11	19	3	33			
Employment status							
Full-time	27	47	3	33			
Part-time	3	5	0	0	0.895	2	<.64
Unemployed	27	47	6	67			
Legal charges pending	16	28	2	22	0.001	1	<.97
Coexisting diagnoses[b]							
Substance abuse	16	28	3	33	0.005	1	<.94
Major depression	18	32	4	44	0.145	1	<.70
Personality disorder	11	19	2	22	0.060	1	<.81
Psychosis	2	3	0	0	0.226	1	<.63

[a]For the subjects who were and were not followed up, there was no significant difference in mean±SD age (44.14±11.10 versus 39.56±8.43 years; t=1.18, df=64, p<.12) or education (13.10±2.28 versus 13.22±2.65; t=−0.15, df=64, p<.44).
[b]Some subjects had more than one coexisting diagnosis.

TABLE 2. Pre- and Posttreatment Scores of Pathological Gamblers on Gambling Behavior and Psychiatric Status Schedule

Measure	Month Before Treatment N	Mean	SD	Sixth Month After Treatment N	Mean	SD	t (paired observations)	df	p
Patient report measures									
Time Line Follow Back Month									
Number of days gambling	57	15.70	9.87	57	4.74	9.20	6.68	56	<.001
Weighted score of number of days gambling	57	31.27	21.06	57	7.30	15.94	7.96	56	<.001
Gambling Behavior Survey									
Money spent gambling per week	50	$738	$1,058	56	$70	$298	4.59	49	<.001
Number of Gamblers Anonymous meetings attended per month	53	1.04	2.28	55	4.02	5.21	−3.99	51	<.001
Psychiatric Status Schedule									
Subjective distress	56	29.12	11.08	54	11.46	12.67	8.91	52	<.001
Behavioral disturbance	54	1.17	2.04	45	1.76	5.48	−0.75	43	<.23
Impulse control disturbance	56	5.34	5.43	54	1.37	2.67	5.42	52	<.001
Reality testing disturbance	54	2.61	4.16	54	1.46	3.17	2.37	52	<.01
Summary role impairment	55	60.85	10.07	48	47.66	10.81	6.56	45	<.001
Wage earner role	41	4.54	2.73	36	0.89	1.89	7.10	31	<.001
Alcohol abuse	54	4.11	8.11	54	1.33	4.46	2.90	50	<.003
Suicide-self mutilation	53	1.28	1.21	54	0.19	0.55	7.27	52	<.001

contact the patient and administer the Psychiatric Status Schedule, Time Line Follow Back Month, and Gambling Behavior Survey to him on the telephone. Telephone interviews were used because the program draws patients from throughout the country. Sixty of the 66 patients studied lived more than 200 miles from the program. None of the 66 was provided outpatient care from our program. At the same time an attempt was also made to contact the collateral informants and readminister the modified Gambling Behavior Survey. Repeated attempts, including evenings and weekends, were made in order to track the maximum number of patients and collateral informants possible. While an attempt was made to have the follow-up interviews conducted by the initial interviewer, the logistics of scheduling necessary to contact most patients often made this difficult.

RESULTS

Six-month follow-up interviews were conducted with 57 patients (86%). Table 1 presents demographic and clinical data on the patients followed up and on those not located. Diagnostic information was based on the clinical decisions of the treatment staff recorded in their assessments in the medical record. The subjects located for follow-up did not differ significantly from those not located on any of these variables. Six-month follow-up interviews were conducted with collateral informants of 46 of the patients followed up (80%). Thirty-six of the collateral informants (78%) were women; 24 (52%) were spouses of the gambler, nine (20%) were immediate family members, eight (17%) were Gamblers Anonymous sponsors or counselors, and five (11%) were close friends.

Table 2 presents the scores of the patients' ratings on the major variables extracted from the Time Line Follow Back Month and the Gambling Behavior Survey. All measures reflected considerable improvement in gambling behavior on 6-month posttreatment follow-up compared to pretreatment levels. The number of patients rated on some of the measures varied because some questions on the Gambling Behavior Survey were not applicable to some patients or the informant's recollection for the period was not adequate to obtain a reliable report.

The reports of the collateral informants on the measure of the number of days gambled in the sixth month after treatment correlated with the reports of the patients ($r=.82$, $df=44$, $p<.01$). Thirty-two of the 57 patients interviewed (56%) reported abstinence for the full 6 months after treatment. Thirty-eight (67%) reported abstinence during the sixth month after treatment. Twenty-five of the 46 collateral informants interviewed (54%) reported that the patient had been abstinent for the full 6 months after treatment. The reports of the collateral informants on whether the patient was totally abstinent for the 6-month period after treatment were highly consistent with the patient's own report. In only two cases did the patient and informant disagree on whether the patient had been abstinent; interestingly, in both cases the patient reported gambling while the informant reported abstinence.

Table 2 also presents the scores of the patients on the summary scales of the Psychiatric Status Schedule and on the suicide-self mutilation, wage earner role, and alcohol abuse scales. Subjective distress is a composite of the following individual scales: depression-anxiety, suicide-self mutilation, somatic concern, social isolation, and daily routine-life impairment. Behavioral disturbance is a composite of the following individual scales: inappropriate affect-appearance-behavior, interview belligerence, agitation-excitement, lack of emotion, speech disorganization, and disorientation-memory. Impulse control disturbance is a composite of the following individual scales: antisocial impulses or acts, drug abuse, and reported overt anger. Reality testing disturbance is a composite of the following individual scales: grandiosity and suspiciousness-persecution-hallucinations. Summary role impairment is computed from individual ratings of the patient's functioning in whichever of the following roles apply: wage earner, student, mate, parent, and housekeeper. In all cases, higher scores indicate greater impairment.

Results for the alcohol abuse scale are presented separately because it is not included in any of the summary scales and because of earlier work on the relationship between substance abuse and gambling (5), making the possibility of substituting addictions important in analyzing outcome. Results for the suicide-self mutilation scale are presented separately, even though it is also included in subjective distress, because of the earlier reported high rate of suicide in pathological gamblers and the special importance of this dimension to treatment planning (3). Scores for wage earner role are presented separately because of the importance of vocational rehabilitation to abstinence.

The nine patients not followed up did not differ significantly, before treatment, from the followed-up patients on any of the variables reported in table 2.

DISCUSSION

Although this study attempted to provide as thorough an outcome evaluation as feasible within the confines of an active treatment program, certain limitations are inherent. There was no external no-treatment control group due to concerns with denying treatment to patients in dire need. Consequently, the contribution of spontaneous recovery is unknown. The patients were used as their own controls in the design, and while it might be argued that they would be at their worst just before seeking treatment, their histories invariably documented long periods of continuous, serious pathological gambling. Subjects averaged more than 18 years of pathological gambling, with the longest period of abstinence being, on the average, less than 11 months.

Despite the design factors that must modulate interpretation of the results, the study does establish that, on the basis of a high rate of follow-up, a sizable proportion of seriously impaired pathological gamblers were able to maintain abstinence and general behavioral improvement after an intensive, short-term, structured treatment program. We believe that these results clearly support the proposition that pathological gambling is a treatable disorder. Given the increasing popularity of gambling as a recreational option and the expected concomitant increase in the frequency of pathological gambling, it is important for clinicians, regardless of their treatment setting, to become skilled in diagnosing the disorder in their patients and providing or referring them for treatment.

Participation in Gamblers Anonymous is stressed in our program. In the month before follow-up, 74% of the patients who were abstinent had attended at least three Gamblers Anonymous meetings, compared to 42% of those who were not abstinent. As a group the abstinent patients attended significantly more meetings ($\text{mean}\pm SD=5.90\pm6.13$) than the nonabstinent patients (1.58 ± 1.93) ($t=3.32$, $df=53$, $p<.001$). Of the followed-up patients, only five received any mental health outpatient care in the 6 months after treatment in our program, and one received inpatient care for depression. Clearly, participation in Gamblers Anonymous, which was the primary aftercare resource for these patients, was an important factor in their continued abstinence.

The results of this study compare favorably with reported abstinence after treatment for alcohol and drug abuse, where 6-month abstinence rates for similar populations have ranged from 23% to 44% (21–23).

The high scores of the gamblers on depression and suicidal tendencies, as measured by the Psychiatric Status Schedule at the time of admission, are consistent with earlier reports (3, 4). The improvement on these dimensions and decrease in gambling behavior after treatment are encouraging. It must, however, be noted that although the magnitude of the correlation at 6-month follow-up between depression and abstinence was significant ($r=.45$, $df=55$, $p<.01$), it was far from perfect. This is reflective of a subgroup of gamblers whose depression did not lift despite abstinence. Seven of the patients who were abstinent (18%) reported significant improvement in work and family life, in addition to their abstinence, but still were significantly depressed. This finding is consistent with the possibility that while depression is situationally related to the effects of gambling behavior for one subgroup of pathological gamblers, it is independent of the gambling for another subgroup, for whom the gambling may in fact be an attempt to cope with the primary problem of depression.

Data collection for a 12-month follow-up is continuing, as is an analysis of the psychological measures taken on program entry to determine which may be predictive of later positive outcome.

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Treatment of a Patient With Seasonal Premenstrual Syndrome

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The authors identified a patient who had premenstrual syndrome (late luteal phase dysphoric disorder) only in the fall and winter and was virtually asymptomatic during the spring and summer. On the basis of previous experience with seasonal affective disorder, they treated the patient with bright artificial light, which reversed her symptoms. On subsequent occasions they reversed this treatment effect with oral melatonin administration and found that propranolol and atenolol, β-antagonists that inhibit the production of melatonin, had a therapeutic effect similar to that of light. They discuss the implications of these findings in relation to the importance of melatonin as a mediator of seasonal rhythms in biology.
(Am J Psychiatry 1987; 144:762–766)

Premenstrual syndrome (late luteal phase dysphoric disorder) is characterized by cyclic mood changes occurring in synchrony with the menstrual cycle (1). Depression or dysphoria generally occurs premenstrually and improves shortly after the onset of menses. Seasonal affective disorder, a condition of cyclic mood changes found predominantly in women (2), is characterized by the occurrence of depression in fall and winter and remissions in spring and summer. Women with seasonal affective disorder frequently have premenstrual syndrome as well. Besides typical symptoms of depression, patients with seasonal affective disorder and those with premenstrual syndrome have other symptoms in common, including overeating, oversleeping, carbohydrate craving, and lethargy (1, 2). In this paper we describe a patient with a history of premenstrual syndrome in the fall and winter. She would not qualify for a diagnosis of seasonal affective disorder in that she was asymptomatic in the winter during the follicular phase of her menstrual cycle.

Seasonal affective disorder resembles a variety of annual rhythms found in animals (3), both in its cyclic relationship to the seasons and in its capacity to be modified by changing environmental lighting conditions (2, 4). Extending the photoperiod with bright (2,500 lux), full-spectrum light has been shown to reverse depressive symptoms in patients with seasonal affective disorder (5). In this paper we describe a similar treatment regimen used for our patient with seasonal premenstrual syndrome.

The influence of the photoperiod on seasonal reproductive cycles in animals has been shown to be mediated by suppression of the nocturnally secreted pineal hormone melatonin (6). This hormone can be suppressed by light in both animals (7) and humans (8), although in the latter case high-intensity light is required. While it appears unlikely that melatonin plays a central role in mediating the effects of seasons and phototherapy on mood in most patients with seasonal affective disorder, it is conceivable that its production in winter may aggravate some of the symptoms of seasonal affective disorder (9) and its suppression by light may alleviate these symptoms. In our patient with seasonal premenstrual syndrome, we explored the effects of light, melatonin, and the β-adrenergic antagonists propranolol and atenolol, which have been found to block melatonin release in a series of interventions during the patient's premenstrual phase (10, 11).

CASE REPORT

Ms. A, a 24-year-old woman, presented with a history of severe 2-week premenstrual depressions during the fall and winter months. She was asymptomatic during the summer months and during the follicular phase of her menstrual cycle in the winter. During her depressed periods the patient experienced fatigue, lethargy, irritability, loss of appetite, insomnia, diurnal variation in mood (worse in the morning), social withdrawal, and suicidal ideas. Depressions remitted within a few days after the onset of menses and were absent during the summer. Her father had a history of manic-depressive illness. The patient reported no other affective episodes apart from the premenstrual symptoms. Her menses occurred regularly approximately every 28 days, with slightly shortened cycles (26 days) in the winter.

METHOD AND RESULTS

To document mood state, weekly scores on the 21-item Hamilton Rating Scale for Depression were obtained during an asymptomatic summer month and

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TABLE 1. Hamilton Depression Ratings of a Patient With Seasonal Premenstrual Syndrome

Experiment	Condition	Duration (cycle days)	Time of Rating (cycle day)	Hamilton Depression Scale Rating
1	Baseline	To −9	−9	30
	Bright light	−8 to −1	−1	10
2	Baseline	To −9	−9	25
	Bright light and placebo	−8 to −5	−5	10
	Bright light and melatonin, 1.6 mg over 6 hours	−5 to −2	−2	26
	Withdrawal from lights and melatonin	−2 to −1	−1	32
3	Baseline	To −14	−14	25
	Placebo	−14 to −8	−8	37
	Propranolol, 80 mg/day	−8 to −4	−4	5
	Propranolol, 40 mg/day (different cycle)	−8 to −1	−1	15
4	Baseline	To −10	−10	25
	Atenolol, 50 mg/day	−9 to −1	−1	11
	Placebo (different cycle)	−9 to −1	−1	35

subsequently during the fall and winter months. Subjects and raters were instructed to evaluate the Hamilton scale items on the basis of the patient's predominant state during the previous week. During interventions, ratings were done by blind raters with an established interrater reliability of .90. Hormone assays for serum estradiol, progesterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, cortisol, and thyroid-stimulating hormone (TSH) were done with standardized radioimmunoassay techniques. Melatonin was assayed by the technique of Tamarkin et al. (12). Informed consent was obtained after the procedures had been explained.

Experiment 1: An Initial Uncontrolled Trial of Phototherapy

After the onset of depressive symptoms in the winter, baseline ratings were obtained and then a trial of phototherapy was undertaken. Each night from 6:00 to 11:00 p.m. after the onset of the patient's symptoms, from the premenstrual period until the onset of menses, bright, full-spectrum light (2,500 lux) was administered at home to the patient, who sat 3 feet away from the light source (eight 40-watt fluorescent bulbs) and was told to glance at it approximately every few minutes. Baseline Hamilton ratings in the premenstrual phase during a winter month without treatment were 25 and 28. The subsequent Hamilton score during the follicular phase was 0. In the following premenstrual phase, the patient responded to the initial trial of phototherapy (table 1), as indicated by a marked drop in the Hamilton score after 1 week (from 30 to 10).

Experiment 2: A Controlled Trial of Phototherapy—Light Plus Placebo Versus Light Plus Melatonin

The following month, in an inpatient setting, a controlled trial of light was administered with placebo and then with melatonin during the premenstrual phase of the patient's cycle in order to determine if melatonin could reverse the therapeutic effect of light. Overnight melatonin profiles were obtained every hour from 5:00 p.m. to 7:00 a.m. during 1) the follicular phase of the cycle, 2) the luteal phase, 3) administration of light and placebo in the premenstrual phase, and 4) administration of light and melatonin in the premenstrual phase. A total of 1.6 mg of melatonin was given orally in 200-μg doses hourly from 5:00 to 10:00 p.m. and 400 μg were given at 11:00 p.m. Finally, light and melatonin were discontinued and the patient was maintained on a regimen of placebo alone. During each intervention, 7:00 a.m. blood samples were drawn for estradiol, progesterone, FSH, and LH assays to determine cycle phase and to document ovulation. Cortisol, prolactin, and TSH values were obtained hourly with the melatonin samples to determine the effects of light on these hormones.

The patient improved during treatment with light plus placebo (Hamilton score decrease from 25 to 10) and relapsed when melatonin was given with the light (score of 26). When lights and melatonin were discontinued, the patient returned to her previous level of premenstrual depression (Hamilton score of 32).

Melatonin profiles done across the menstrual cycle are illustrated in figure 1.

There was a tendency for light to suppress melatonin in the early evening, with a rebound later in the night. There was a slight delay in the onset of melatonin secretion in the premenstrual phase compared to the follicular phase. In addition, as has been reported in some depressed populations, melatonin levels were unusually low compared to published normal values (13–17).

The remarkable endocrine data were as follows: there was no significant difference in melatonin profiles between the baseline follicular and premenstrual phases ($t=0.89$, $df=10$, n.s., paired t test). An analysis of variance (ANOVA) with repeated measures was done on the melatonin profiles for each condition. The conditions were 1) the baseline follicular phase, 2) the baseline premenstrual phase, 3) the light and placebo treatment, and 4) the propranolol treatment. An a priori decision was made not to include the condition of melatonin administration because we expected that

FIGURE 1. Nocturnal Melatonin Profiles in a Patient With Seasonal Premenstrual Syndrome

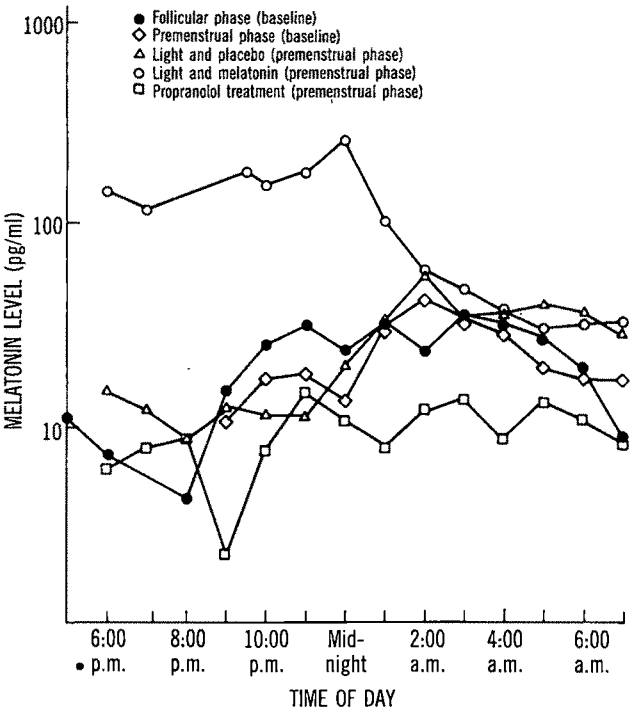
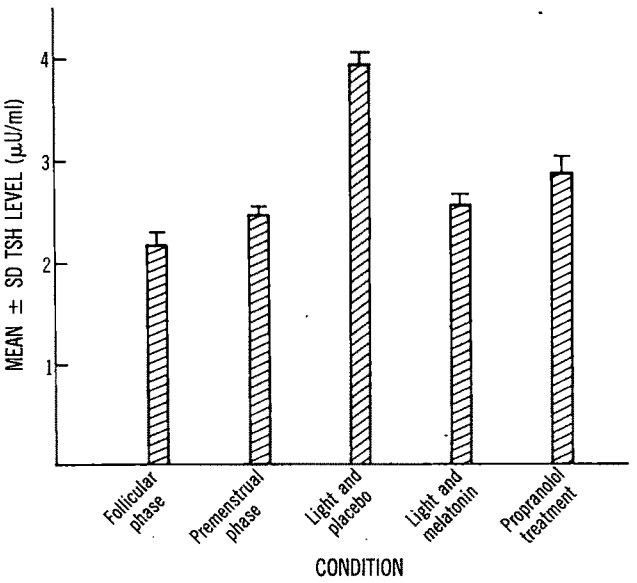


FIGURE 2. Nocturnal TSH Levels in a Patient With Seasonal Premenstrual Syndrome



this condition would be different from the other melatonin profiles. There were significant main effects for both condition ($F=14.18$, $df=3, 20$, $p<.0001$) and time of day ($F=5.72$, $df=4, 20$ by using 8 hours with 2 hours/cell, $p<.01$). ANOVA indicated no significant interaction between condition and hour ($F=2.16$, $df=12, 20$, $p=.06$).

For TSH, a two-factor (condition and hour) ANOVA showed a significant main effect for condition ($F=23.94$, $df=4, 20$, $p<.0001$). The mean±SD levels for TSH in each condition are presented in figure 2. There was no significant main effect for time of day ($F=0.33$, $df=3, 20$ with 2 hours/cell, n.s.), nor was there a significant Time of Day by Condition interaction ($F=1.2$, $df=12, 20$, n.s.). There was no significant difference between baseline follicular and premenstrual TSH values ($t=1.79$, $df=7$, n.s., paired t test).

For prolactin, significantly higher values were found during the follicular phase (mean±SD=19.05±2.05 ng/ml) than during the premenstrual phase (9.22±3.54 ng/ml) ($t=10.83$, $df=7$, $p<.001$, paired t test). There was a significant main effect of time of day ($F=3.69$, $df=7, 20$, $p<.006$, ANOVA) but no significant interaction between condition and time of day ($F=1.03$, $df=12, 20$ by using two entries/cell, n.s.).

Progesterone levels (>5 ng/ml) in the luteal phase indicated that ovulation had occurred.

Experiment 3: Treatment With Propranolol

We hypothesized that if light acted by suppressing melatonin secretion, then propranolol, a β-antagonist that inhibits the synthesis and release of melatonin from the pineal (10), should have a comparable effect. The patient took either placebo or propranolol, 40 mg orally at 6:00 and 9:00 p.m. (after an initial test dose of 20 mg), in a double-blind crossover trial after the onset of her depressive symptoms in the subsequent winter month. Because of side effects, the crossover trial was repeated during a later menstrual cycle, with a lower dose (20 mg at 6:00 and 9:00 p.m.).

Propranolol (80 mg) reversed the patient's premenstrual depression (Hamilton score decrease from 25 to 5). The 40-mg dose was also effective in reducing her depressive symptoms (Hamilton score change from 37 to 15). In contrast to phototherapy, which suppressed melatonin only in the first half of the night, propranolol suppressed melatonin throughout the night (see figure 1).

Experiment 4: Treatment With Atenolol

The following winter we repeated light treatment with equally good effect. During a subsequent trial we found that 50 mg/day of atenolol (administered at 4:00 p.m.), a β-antagonist that crosses the blood-brain barrier in lower concentrations, was as effective as propranolol (Hamilton scale decrease from 25 to 11). By this time, since so many interventions had been made, we felt a placebo-only trial was indicated. During the placebo trial the patient's Hamilton score increased from 28 to 35 in the premenstrual period.

DISCUSSION

Seasonal affective disorder and premenstrual syndrome are both cyclic forms of affective disorders.

Some women suffer from both seasonal affective disorder and premenstrual syndrome. In this patient, there appeared to be an interaction of seasonal and menstrual rhythms such that the cyclic symptoms of premenstrual syndrome were experienced only in the fall and winter. A striking analogy to our patient's illness can be found in the patients described by Gjessing (18), in whom the cyclic symptoms of periodic catatonia (or rapid cycling manic-depressive illness) were expressed only in the fall and winter.

In seasonally breeding animals, changes in the pattern of melatonin secretion appear to mediate the effects of seasonal changes in day length on the neuroendocrine reproductive axis (19–23). The effects of light are transmitted by the retinohypothalamic tract and the suprachiasmatic nuclei of the anterior hypothalamus through a multisynaptic pathway to the pineal, where β-adrenergic stimulation triggers nocturnal melatonin production and release (24). Melatonin then acts on the reproductive neuroendocrine axis, possibly by altering the sensitivity of gonadotropin- and prolactin-secreting cells to feedback effects of estrogen, and brings about changes in the reproductive system specific to the species (25).

In addition to its role in seasonal rhythms, melatonin affects the reproductive system in other ways. Decreases in melatonin levels at estrus (26) appear to have a permissive effect on the LH surge and ovulation (27, 28). Evidence indicating a role for melatonin in the human menstrual cycle is scant and inconsistent (17, 29–31).

Several observations suggest that changing patterns of melatonin secretion may have been partly responsible for this patient's depressive symptoms: symptoms were alleviated by high-intensity light and by propranolol and atenolol, all of which inhibit the synthesis and release of melatonin by the pineal (8, 10, 11). Conversely, exogenous melatonin reversed the therapeutic effect of light. Induction of symptoms of premenstrual syndrome by melatonin administered during the summer months would lend further support to the hypothesis that melatonin is involved in the pathogenesis of seasonal premenstrual syndrome. Melatonin appears to have played a more important role in this patient's illness than has been found to be the case in most patients with seasonal affective disorder (32). In animals, melatonin has been shown to be an important mediator of seasonal influences on reproduction but not on other functions such as hibernation. Melatonin-mediated seasonal rhythms in reproduction may be suitable animal models for seasonal premenstrual syndrome but not for seasonal affective disorder, which may, in this respect, be more akin to hibernation. Although our experiments focused on the possible role of melatonin in the mechanism of action of light, it may have been the phase-delaying effects of evening light on the patient's circadian rhythms that contributed to the therapeutic response to light (33). Elevation of TSH during light treatment raises the possibility that this hormone may also mediate the effect of phototherapy. Some studies in animals suggest that light affects the thyroid axis (34, 35).

Results obtained from a single case study cannot be generalized to other patients with premenstrual syndrome. Such an investigation, however, can serve a useful pilot function. Currently, we have identified other patients with seasonal premenstrual syndrome and plan further investigations into the nature of the illness based on these preliminary findings.

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Covariation of Criteria Sets for Avoidant, Schizoid, and Dependent Personality Disorders

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Avoidant personality disorder was a new addition to DSM-III. *Reaction to its inclusion was mixed. Critics cited the lack of empirical data and the overlap with schizoid disorder. The authors consider the overlap and covariation among avoidant, schizoid, and dependent symptoms and diagnoses in a sample of 84 inpatients diagnosed by using a semistructured interview. Items for avoidant disorder covaried with criteria for dependent disorder but not with criteria for schizoid disorder. The authors point out the implications of these results for the revision of* DSM-III *(*DSM-III-R*).*

(Am J Psychiatry 1987; 144:767–771)

Avoidant personality disorder was a new diagnostic category introduced by *DSM-III*. Although some (1, 2) supported its inclusion, critics (3–6) pointed to the lack of empirical data and doubted whether it could be reliably differentiated from schizoid and dependent personality disorders. Research since the publication of *DSM-III* has indicated that it is much more frequently diagnosed in clinical settings than is schizoid disorder (5, 7–9), but there are few relevant data on the differential diagnosis of avoidant, schizoid, and dependent personality disorders.

Kass et al. (8) found the highest correlation in personality disorder ratings between avoidant and dependent disorders (r=.43). Avoidant and schizoid disorders did not correlate highly (r=.17), nor did dependent and schizoid disorders (r=.03). Millon (10) reported a correlation of .76 between the avoidant and schizoid-asocial scales of the Millon Clinical Multiaxial Inventory, a correlation of .59 between the avoidant and the dependent-submissive scales, and a correlation of .40 between the dependent-submissive and the schizoid-asocial scales, but it is not clear to what extent the Millon Clinical Multiaxial Inventory scales adequately measure the *DSM-III* syndromes. The *DSM-III* diagnosis of avoidant personality disorder is based heavily on Millon's typology (3), but the Millon Clinical Multiaxial Inventory may not provide a valid measure of schizoid and dependent disorders (11). More importantly, the correlations reported by Millon were forced by the overlap among scales. The avoidant and schizoid-asocial scales share 36% of their items, the avoidant and dependent-submissive scales share 22%, and the dependent-submissive and schizoid-asocial scales share only 6%.

The present study is, to our knowledge, the first empirical analysis of the differential diagnosis of avoidant personality disorder. We consider the diagnostic efficiency of the criteria for avoidant, schizoid, and dependent personality disorders for the diagnosis of avoidant personality disorder; the covariation of each criterion with the criteria sets for avoidant, schizoid, and dependent disorders; and the internal covariation of the criteria for avoidant disorder.

METHOD

Subjects were 84 inpatients from short-term units of a state hospital. Sampling was conducted over an 18-month period and was limited to those patients who, on the basis of chart review and a clinical interview, did not meet the *DSM-III* criteria for schizophrenia, major affective disorder, or a chronic organic mental disorder; were capable of participating in a meaningful interview (e.g., not currently psychotic); and met *DSM-III* criteria for at least one personality disorder. The mean±SD age of the patients was 28.2±8.2; 54 (64%) of the patients were men; 77 (92%) were Caucasian; 14 (17%) were employed; 29 (35%) had a high school diploma; and 38 (45%) were single, 30 (36%) were divorced, and 14 (17%) were currently married.

Each patient was interviewed by a college senior for up to 2 hours using a semistructured interview, the Personality Interview Questions (12). This interview provides questions for each of the 81 symptoms for all 11 *DSM-III* personality disorders. Each symptom was rated on a 1–9-point scale: 1 indicated that the symptom was absent, 2–4 indicated a degree of severity below clinical threshold, and 5–9 indicated a degree of

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TABLE 1. Prevalence, Kappa, Interrater Reliability, and Diagnostic Efficiency of Avoidant, Dependent, and Schizoid Symptoms for Diagnosis of Avoidant Personality Disorder in 84 Inpatients With Personality Disorders

Symptom	Patients With Symptom		Kappa	Interrater Reliability (r)	Diagnosis of Avoidant Personality Disorder	
	N	%			Positive Predictive Power	Negative Predictive Power[a]
Avoidant personality disorder						
Hypersensitivity to rejection	58	69	.59	.51	.48	1.00
Unwillingness to enter relationships	48	57	.73	.76	.58	1.00
Social withdrawal	65	77	.62	.65	.43	1.00
Desire for affection and acceptance	60	71	.73	.70	.47	1.00
Low self-esteem	58	69	.66	.81	.48	1.00
Dependent personality disorder						
Passively allows others to assume responsibility	54	64	.72	.79	.46	.90
Subordinates own needs	48	57	.68	.72	.46	.83
Lacks self-confidence	62	74	.54	.80	.44	.95
Schizoid personality disorder						
Emotional coldness and aloofness	20	24	.85	.71	.10	.59
Indifference to praise, criticism, or others' feelings	13	15	.74	.68	.00	.61
Close friendships with no more than one or two persons	66	79	.51	.70	.33	.67
No schizotypal eccentricities of speech, behavior, or thought	56	67	.73	.65	.32	.64

[a]These rates for the avoidant symptoms equal 1.00 because the *DSM-III* monothetic criteria set requires that every patient have each symptom to receive the diagnosis.

severity above clinical threshold. The final rating was determined by consensus with one of us (T.A.W.), who used the ratings to determine *DSM-III* diagnoses. (Details regarding the Personality Interview Questions are available from Dr. Widiger at the University of Kentucky, and further information regarding the training of interviewers is presented elsewhere [13].) Sixty-seven of the interviews were audiotaped for reliability testing.

Lay interviewers were used to minimize the effect of clinical biases on the ratings (12). These interviewers were blind to the research hypotheses, had no expectations regarding the results, and remained largely unaware of the *DSM-III* criteria sets because the sets were reorganized by the Personality Interview Questions. Previous training and subsequent supervision of problematic ratings by a clinician compromised the advantages gained by using lay interviewers but helped ensure clinical validity. The Millon Clinical Multiaxial Inventory was administered to 53 of the patients to provide convergent validity for the avoidant personality disorder ratings. To our knowledge, this is the first semistructured interview study to provide self-report data to support the convergent validity of the ratings.

RESULTS

Kappas for the avoidant, dependent, and schizoid diagnoses were .67, .65, and .71, respectively. These rates are acceptable and consistent with other research using semistructured interviews (9). Cronbach's alpha statistic, which provides an estimate of the mean of all possible split-half correlations, for the avoidant, dependent, and schizoid diagnoses was .67, .73, and .38, respectively. Twenty-eight (33%) of the patients met *DSM-III* criteria for avoidant disorder, 40 (48%) for dependent disorder, and seven (8%) for schizoid disorder. Twenty (71%) of the 28 patients with avoidant disorder met the criteria for dependent disorder, and 20 (50%) of the 40 patients with dependent disorder met the criteria for avoidant disorder. None of the patients with schizoid disorder met the criteria for avoidant or dependent disorders, a result in part of the small number of patients with schizoid disorder.

Eighteen (64%) of the 28 patients with avoidant disorder and 35 (63%) of the 56 patients with any other personality disorder completed the Millon Clinical Multiaxial Inventory. The highest personality scale elevation for the avoidant group was on the avoidant scale: patients with avoidant disorder had a mean± SD score of 94±21, significantly higher than that of the other patients (70±34) ($t=2.7$, $df=51$, $p<.01$). The correlation between the number of avoidant symptoms shown by each patient and their score on the avoidant scale was .53 ($p<.01$; $N=53$). True positive and true negative rates for the recommended cutoff score of 85 were 78% and 54%, respectively. The avoidant group also obtained significantly higher elevations on the anxiety scale (mean±SD=96± 22)($t=2.9$, $df=51$, $p<.01$), the somatoform scale (84±20) ($t=3.9$, $df=51$, $p<.01$), and the dysthymia scale (91±26) ($t=2.7$, $df=51$, $p<.01$). These results lend convergent validity to the avoidant personality disorder ratings.

Table 1 presents the prevalence, kappa, interrater reliability, positive predictive power rate, and negative predictive power rate (14) for the *DSM-III* criteria for

TABLE 2. Correlation of Number of Avoidant, Dependent, and Schizoid Symptoms With Symptoms of 84 Inpatients With Personality Disorders

Symptom	Correlation (r)		
	Avoidant Symptoms[a]	Dependent Symptoms[a]	Schizoid Symptoms[a]
Avoidant personality disorder			
Hypersensitivity to rejection	.49[b]	.45[b]	−.24[c]
Unwillingness to enter relationships	.54[b]	.52[b]	−.26[c]
Social withdrawal	.21[d]	.00	.33[b]
Desire for affection and acceptance	.10	.47[b]	−.48[b]
Low self-esteem	.49[b]	.56[b]	−.23[c]
Dependent personality disorder			
Passively allows others to assume responsibility	.50[b]	.68[b]	−.41[b]
Subordinates own needs	.37[b]	.59[b]	−.44[b]
Lacks self-confidence	.61[b]	.37[b]	−.16
Schizoid personality disorder			
Emotional coldness and aloofness	−.10	−.34[b]	.31[b]
Indifference to praise, criticism, or others' feelings	−.26[c]	−.33[b]	.35[b]
Close friendships with no more than one or two persons	.09	−.15	.20[d]
No schizotypal eccentricities of speech, behavior, or thought	−.08	−.10	.06

[a]Excluding the symptom for the correlations involving that symptom (e.g., for the correlation of hypersensitivity to rejection with number of avoidant symptoms, the total number was equal to the total number of avoidant symptoms minus hypersensitivity to rejection).
[b]$p<.01$, two-tailed.
[c]$p<.05$, two-tailed.
[d]$p<.05$, one-tailed.

TABLE 3. Intercorrelations of Avoidant Symptoms in 84 Inpatients With Personality Disorders

Symptom of Avoidant Personality Disorder	Correlation (r)			
	Hypersensitivity to Rejection	Unwillingness to Enter Relationships	Social Withdrawal	Desire for Affection and Acceptance
Unwillingness to enter relationships	.49[a]			
Social withdrawal	.28[a]	.39[a]		
Desire for affection and acceptance	.19[b]	.17	−.21[b]	
Low self-esteem	.53[a]	.50[a]	.32[a]	.23[c]

[a]$p<.01$, two-tailed.
[b]$p<.05$, one-tailed.
[c]$p<.05$, two-tailed.

avoidant, dependent, and schizoid personality disorders. The prevalence rates were comparable, with the exception of two of the schizoid items, emotional coldness and aloofness and indifference to praise or criticism. Kappas for all symptoms were acceptable, ranging from .51 to .85. Interrater reliability determined by using the 1–9 dimensional ratings for each symptom ranged from .51 to .81 (all p values<.001).

Among avoidant symptoms, social withdrawal had the lowest positive predictive power rate, .43. The negative predictive power rates for the symptoms of dependent disorder's diagnosis of avoidant personality disorder were uniformly high, and the positive predictive power rates exceeded those for social withdrawal and approximated the rates for the remaining avoidant items. In comparison, all four schizoid symptoms had low positive predictive power and negative predictive power rates in diagnosing avoidant personality disorder. In the case of the criteria of emotional coldness and aloofness and indifference to praise or criticism in schizoid personality disorder, the low negative predictive power values may reflect the low base rate for these symptoms.

The correlations of each symptom's 1–9 dimensional rating with the number of avoidant, dependent, and schizoid symptoms shown by each patient (the symptom list) are presented in table 2. If the symptom was part of the disorder's diagnostic criteria, it was excluded from the symptom list for the correlations involving that symptom. The symptom lists were used rather than the presence or absence of the disorder because of the small number of patients with schizoid disorder. Few patients met all of the criteria for schizoid disorder, but there was substantial variation in the total number of symptoms.

Among avoidant criteria, social withdrawal and the desire for affection and acceptance had the lowest correlations with the avoidant symptom list. Each of the avoidant items correlated significantly with the dependent symptom list, with the exception of social withdrawal. All of the avoidant symptoms were negatively correlated with the schizoid symptom list, with

the exception of social withdrawal, which obtained a significant positive correlation. Each dependent symptom was positively correlated with the avoidant symptom list, and two were negatively correlated with the schizoid symptom list. The schizoid items emotional coldness and aloofness and indifference to praise or criticism were negatively correlated with the dependent symptom list, and indifference to praise or criticism was negatively correlated with the avoidant symptom list, despite the small number of patients with these symptoms.

Table 3 presents the intercorrelations among the avoidant symptoms calculated on the 1–9-point dimensional ratings. Social withdrawal was significantly positively correlated with unwillingness to enter relationships, hypersensitivity to rejection, and low self-esteem and negatively correlated with desire for affection and acceptance. Desire for affection and acceptance was not highly correlated with any avoidant symptom.

DISCUSSION

Critics of the diagnosis of avoidant personality disorder have suggested that it cannot be reliably differentiated from the diagnosis of schizoid personality disorder because the only distinction was desire for affection and acceptance (3, 4, 6). However, there appears to be little difficulty in differentiating these two disorders. All but one of the avoidant symptoms was negatively correlated with the schizoid symptom list. The only feature they shared was social withdrawal, and it may occur for different reasons. The avoidant patient is hypersensitive, shy, and insecure, while the schizoid patient is indifferent, aloof, and cold. The differential diagnosis may in fact be a moot issue because the very small number of patients with the schizoid diagnosis found in the current study is consistent with findings from a variety of clinical settings (5, 8, 9). One need not be too concerned about an overlap, because few patients will receive a schizoid diagnosis. However, even if more patients with schizoid disorder are available, the low to negative correlations at the item level will be paralleled by an absence or low degree of overlap in diagnosis.

More concern should perhaps be given to the differential diagnosis of avoidant and dependent personality disorders. In the patients with these diagnoses there was a considerable amount of diagnostic overlap and a high correlation in symptoms. In addition, the dependent symptoms obtained positive predictive power rates almost as high as the avoidant symptoms. The avoidant and dependent personality disorders share interpersonal insecurity, a strong desire for interpersonal relationships, and low self-confidence (5). The abdication of responsibility and subordination of needs of the patient with dependent disorder are not included in the criteria for the avoidant diagnosis, but patients with avoidant personality disorder may often be submissive and acquiescent. The avoidant and dependent disorders are distinguished by the difficulty of the person with dependent disorder in separation and the difficulty of the person with avoidant disorder in initiation, but it is conceivable that a person would have difficulty in both initiating and separating from a relationship. A lonely person who intensely desires involvements is likely to be very fearful of losing a relationship once it has been established. Dependent personality traits have in fact been found in patients with axis I social phobia (15).

The key item in differentiating the avoidant and dependent personality disorders is social withdrawal, a finding consistent with that of Pfohl et al. (9). It is the only item the person with avoidant disorder does not share with the person with dependent disorder. Difficulty in assessing social withdrawal will therefore have a substantial effect on the ability to differentiate these two personality styles. Social withdrawal was more highly correlated with the sum of the items for schizoid disorder than for avoidant disorder. Its relatively low correlation with the other avoidant items reflects the fact that the latter describe an interpersonal insecurity that is as characteristic of dependent patients as it is of avoidant patients. In revising the criteria set for avoidant personality disorder, emphasizing or expanding the criterion of social withdrawal should be considered (9).

The forthcoming revision of the *DSM-III* criteria for avoidant personality disorder (*DSM-III-R*) will include additional features of the "phobic character," such as being fearful of being embarrassed, reticence in social situations, and a tendency to exaggerate the potential difficulties in everyday life (7), and will delete the nonspecific item of desire for affection and acceptance. These revisions will increase the distinction between the easily differentiated avoidant and schizoid disorders, but they may not help distinguish avoidant from dependent disorder. In *DSM-III-R*, only five of seven symptoms will be necessary for the diagnosis, allowing a patient to meet the criteria for avoidant disorder without being socially withdrawn. Since this is the only item that currently distinguishes avoidant from dependent disorder, many patients may receive both diagnoses. We have suggested that one or two of the seven criteria be required to anchor the diagnosis to a central construct (16). A useful anchor for the avoidant diagnosis may be social withdrawal.

CONCLUSIONS

Critics of the avoidant diagnosis suggested that it cannot be reliably distinguished from the diagnosis of schizoid personality disorder. The results of the current study indicate little reason for concern, since the disorders share only one item and schizoid disorder is a relatively infrequent diagnosis. The results suggest that the avoidant diagnosis may have more clinical utility than the schizoid because most patients who are

socially withdrawn are anxious and shy rather than cold and indifferent (7). The recent proposal to revise the schizotypal criteria set to emphasize social-interpersonal items would annex additional "schizoid" patients (5). If any diagnosis should be deleted, then, it might be the schizoid.

The forthcoming revision of the avoidant criteria set in *DSM-III-R* will further distinguish the readily differentiated avoidant and schizoid personality disorders, but it may fail to help the more difficult differentiation between the avoidant and dependent personality disorders. It is possible that patients with dependent disorder will also demonstrate a reticence in social situations, a fear of being embarrassed, and a tendency to exaggerate risks. Future revisions of *DSM-III* should probably place more emphasis on social withdrawal, because this item is uncharacteristic of the dependent patient and not highly related to the other avoidant items. These suggestions should be assessed in future studies that employ the final criteria adopted in *DSM-III-R*.

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A Systematic Approach to the Delineation of Personality Disorders

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The author describes a structured approach to the definition of personality disorder diagnoses using traits or generalized behavioral dimensions as the basic unit of definition. Features of personality disorder diagnoses, identified from the clinical literature and rated by psychiatrists for the degree to which they were prototypical of each diagnosis, were classified into 79 behavioral dimensions. A sorting task used to establish whether other clinicians agreed on the classification of highly prototypical features into dimensions yielded satisfactory levels of agreement. A mail survey of a random sample of psychiatrists indicated that these dimensions possessed satisfactory content validity.

(Am J Psychiatry 1987; 144:772–777)

The study of personality disorder is impeded by imprecise definitions and confusion over nomenclature. Basic questions concerning the appropriate structure and content of personality disorder diagnoses have yet to be resolved. Classifications such as *DSM-III* rarely define constructs and criteria but, instead, use terms in their everyday sense, allowing different observers to interpret them differently (1). Inattention to definition is seen in several ways. Synonyms often serve to introduce a superficial distinctiveness among diagnoses, and actual construct distinctiveness is not achieved. For example, the items "socially isolated" in schizotypal personality disorder, "close friendships with no more than one or two persons" in schizoid personality disorder, and "social withdrawal" in avoidant personality disorder all refer to the same behavioral dimension. Difficulties also arise from the failure to specify how similar constructs may be differentiated. For example, how is low self-esteem in avoidant personality disorder different from lack of self-confidence in dependent personality disorder? Or, more subtly, how does hypersensitivity to rejection in avoidant personality disorder differ from hypersensitivity to real or imagined criticism in schizotypal personality disorder?

Progress seems unlikely until distinctive, rigorous concepts are used to specify the components of each diagnosis and explicitly define what is being assessed. A classification system built on careful definitions would ensure that criteria are selected to sample all facets of the diagnosis; possess content validity; are homogeneous, thus contributing to convergent validity; and differentiate between disorders, thus contributing to discriminant validity.

Examination of *DSM-III* reveals an implicit structure in personality disorder diagnoses. *DSM-III* describes diagnostic criteria using constructs that vary in degree of generalization. Some criteria are traits, such as exhibitionistic or egocentric; other criteria are generalized behaviors, such as angry outbursts in histrionic personality disorder; and some criteria are specific behavioral items such as serious absenteeism from work (an average of 3 days or more of lateness or absence per month) in antisocial personality disorder. This hierarchy of constructs is similar to that used by trait theorists to depict the organization of personality (2, 3). If applied consistently, this hierarchy could provide a framework to define personality diagnoses that would establish conceptual continuity with concepts used by academic psychology.

Although the proposals for the revision of *DSM-III*, *DSM-III-R*, involve a simpler model—each diagnosis is defined by a number of specific behavioral criteria—there are good reasons for retaining traits as the basic unit of description and definition. The classification of personality disorders emphasizes behavioral regularities and consistencies that distinguish patients with different disorders. Personality disorder diagnoses do not refer to a single regularity or dimension. Instead, they are typal constructs formed from several traits (4, 5). Thus, borderline personality disorder includes impulsivity, unstable interpersonal relationships, identity disturbance, affective instability, and so on.

The content of definitions—that is, the description and definition of traits and the criteria for assessing them—can be derived empirically by examining the way features cluster in patients or rationally from clinical theory and knowledge (6). Although empirical

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Supported by grant MA-9424 from the Medical Research Council of Canada.

The author thanks Ms. Linda Reiffer and Ms. Adrienne Sheldon for research assistance.

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studies are essential at some point in the development of a valid classification, they are not the most appropriate first step. The problem lies in identifying which characteristics to study. Any empirical study can include only a small sample of the 18,000 trait names identified by Allport and Odbert (6), so that there is a high potential for bias in the initial selection. The potential for bias increases when attempts are made to develop small sets of behavioral criteria, as does *DSM-III-R*. The behavioral manifestations of a given disorder are too numerous to permit a comprehensive catalog of all forms; instead, a small number of behaviors have to be arbitrarily selected as diagnostic criteria, presumably on the basis of an implicit definition of the diagnosis. Thus, neither empirical studies of personality disorder nor classification systems such as *DSM-III* are devoid of theory; they inevitably involve assumptions about which criteria have diagnostic priority. Unfortunately, these assumptions usually remain implicit, whereas the selection of criteria or variables should be informed by explicit definitions.

Because empirical methods presuppose the existence of definitions, the problem of how to develop sound definitions must be addressed. One solution is to derive definitions rationally by using explicitly stated methods, either from a specific theoretical position or from general clinical knowledge. Numerous theoretical positions are available for this purpose, ranging from psychoanalytic perspectives through factor theories to the "circumplex" model of interpersonal behaviors (7, 8). Unfortunately, there is little agreement on the basic dimensions of either normal or abnormal personality. For this reason it may be more appropriate to derive initial definitions from general clinical knowledge, thereby minimizing the bias resulting from adoption of a single theoretical perspective (4). Clinical observation has led to the development of an extensive body of knowledge about these disorders. The task is to organize this knowledge into formal statements to provide the starting point for systematic definitions.

In a previous article (9), I proposed that this could be accomplished through content analysis of the literature and that the important elements of each diagnosis could be identified by using the judgments of random samples of clinicians. This approach assumed that personality disorder diagnoses are prototypical categories—that is, categories defined by characteristics of varying significance. Some characteristics are core features of a diagnosis, and others are more peripheral qualities that may be shared with other diagnoses (8, 10, 11). Thus, the characteristics of a diagnosis form a gradient from highly prototypical to less prototypical characteristics. The fact that psychiatrists agree when rating individual characteristics according to how prototypical they are of a given diagnosis may be used to develop definitions based on highly prototypical features (9). I propose a four-stage process to identify and define the traits of each diagnosis: 1) identification of traits of personality disorder diagnoses listed in *DSM-III* through content analysis of the clinical literature, 2) identification of highly prototypical features by using the judgments of random panels of psychiatrists, 3) development of definitions based on highly prototypical features, and 4) preliminary confirmation of the resulting definitions by using a further sampling of psychiatric opinion. The first two stages have been reported previously (9); this paper describes the next two stages.

METHOD

The identification of traits of each personality disorder diagnosis and the survey of clinical opinion have been described in detail (9). Briefly, the features of each *DSM-III* personality disorder were identified by content analysis of the clinical literature. Lists of the features of each diagnosis were mailed to a random sample of 1,480 psychiatrists in North America; 473 psychiatrists responded. Psychiatrists rated each item on a list of features of a single diagnosis on a 7-point scale according to how prototypical it was of the personality disorder in question; a rating of 7 indicated a highly prototypical feature. The degree of agreement between clinicians, assessed by using Cronbach's alpha coefficient of reliability (12), ranged from 0.81 to 0.96 (median=0.94). This indicates considerable composite agreement in the judging panels regarding the prototypical features of each diagnosis.

Items in each list of features were ranked according to their mean prototypicality rating; the top 25% of items were considered highly prototypical. Examination of the highly prototypical traits for each disorder indicated that many referred to the same behavioral dimension. For example, traits highly prototypical of schizoid personality disorder included "loner, detached, withdrawn, seclusive," "desires minimal personal attachments and obligations, content to be isolated and solitary," and "prefers a peripheral role in relationships." All refer to a behavioral dimension that might be labeled "low affiliation." Consequently, the prototype was reduced to fewer basic categories by grouping together items referring to a common behavioral dimension. To avoid confusion, the following terminology will be used. The items included in the original list of features rated by clinicians will be referred to as "traits." The categories into which similar traits were placed will be referred to as "dimensions." Thus, in the previous example, "loner, detached, withdrawn, seclusive" and "prefers a peripheral role in relationships" are traits, and the category into which they were placed, low affiliation, is a dimension. The following procedure was used to identify and define dimensions.

1. Highly prototypical traits for each disorder were ranked according to their mean prototypicality rating.

2. The highest-ranked trait was used to establish the first dimension. The trait ranked second was included in this dimension if appropriate. If not, an additional dimension was established. The process was continued

TABLE 1. Dimensions Used to Classify Highly Prototypical Traits for Schizoid Personality Disorder

Dimension	Description of Traits	Prototypicality Rating[a]
Low affiliation	Loner, detached, withdrawn, seclusive	6.29
	Prefers a peripheral role in relationships	5.41
Avoidant attachment	Desires minimal personal attachments and obligations; is content to be isolated and solitary	6.13
Defective social skills	Poor or defective interpersonal skills	5.87
	Inability to establish social relationships	6.00
Generalized hypersensitivity	Hypersensitive; acute sensitivity underlies aloofness	5.34
Lack of empathy	Lacks empathy	5.37
	Emotionally cold	5.38
Restricted affective expression	Restricted affectivity	5.79
	Emotionally flat	5.24
	Lacks spontaneity	5.24
Self-absorption	Introverted, self-absorbed	5.87
	Aloof	5.74
	Lack of involvement with everyday events and others' concerns	5.39
Social apprehensiveness	Awkward, uncomfortable, and ill at ease in social situations	5.53
	Timid, shy	5.24

[a]Mean of ratings obtained from 473 surveyed psychiatrists (1=least prototypical; 7=most prototypical).

until all highly prototypical traits were classified.

3. Each dimension was defined. Definitions were based on the traits from which the dimension was derived, and the greatest weight was assigned to traits with the highest prototypicality ratings.

4. The definitions of dimensions related to a single diagnosis were scrutinized for distinctiveness and revised as necessary until an exhaustive and mutually exclusive set of dimensions was established.

5. Steps 1–4 were repeated for all disorders independently.

6. Dimensions were examined across disorders, and definitions were revised to ensure distinctiveness.

7. Less prototypical features—those ranked in the bottom 75% for each diagnosis—were examined to see if they could be classified into the dimensions developed from highly prototypical features. New dimensions were developed as required to create an exhaustive set of dimensions.

8. Definitions of dimensions were reexamined for distinctiveness and revised as necessary.

The process used rational grounds; the dictionary definition of traits and a thesaurus were used to establish dimensions. Reference was also made to personality theories and factor-analytic studies of personality.

RESULTS

Seventy-nine dimensions were required to account for all traits. The number of dimensions required to classify highly prototypical traits for a given disorder ranged from five for avoidant and passive-aggressive personality disorders to 11 for borderline personality disorder. Table 1 illustrates the process for schizoid personality disorder. Thus, the developmental basis of definitional units (dimensions) is explicit. (A list of the 79 dimensions is available from the author on request.)

Each dimension was defined with respect to inclusive characteristics, and, if necessary, the definition specified how the dimension was distinguished from other dimensions. For example, the definition of low affiliation reads, "Avoids social contact; seclusive; unsociable and uninterested in social activities; avoids participating in group activities and declines opportunities to socialize; adopts a peripheral role in social situations; spends considerable time alone." The definition of self-absorption reads, "Preoccupied with inner world; inattentive to people and external events; feels isolated from external world."

Some traits could be appropriately classified into several dimensions because they described aspects of several dimensions. For example, "cold" has connotations of restricted affectivity and lack of empathy. Distinctiveness between dimensions cannot therefore be achieved totally with respect to trait classification. Distinctiveness can, however, be more closely approximated when dimensions are defined by placing greater weight on the more prototypical traits. The dimensions of schizoid personality disorder also illustrate the use of theory: traits relating to social withdrawal were divided into the dimensions of low affiliation and avoidant attachment on the basis of ethological and developmental studies suggesting that attachment and affiliation are separate behavioral systems (13).

CONFIRMATORY STUDIES

The dimensions developed by the procedure described here constitute the basic unit of description and definition. Although the validity of these dimensions will ultimately be established empirically, it is appropriate at this stage to determine whether they successfully represent clinical concepts. This was investigated in two studies. The first established whether clinicians agreed with my classification of traits into dimensions. The second was a further survey of psychiatric opinion to determine whether clinicians agreed that the dimensions were the prototypical features of each disorder.

TABLE 2. Agreement Among 282 Surveyed Psychiatrists on Prototypicality of Features of Patients With Personality Disorders[a]

DSM-III Personality Disorder	Number of Raters	Alpha Coefficient of Reliability of Agreement	Rating			Agreement Between Previous and Current Surveys	
			Mean	SD	Range	Dimensions Identified in First Survey	Dimensions Ranked Highest in Second Survey
Paranoid	31	0.96	4.29	1.16	1.60–6.37	8	6
Schizoid	26	0.93	3.67	1.09	1.46–6.15	8	6
Schizotypical	23	0.94	4.12	1.21	1.43–6.17	10	8
Histrionic	22	0.96	4.41	1.24	1.55–6.91	8	5
Narcissistic	25	0.95	4.33	1.19	1.70–6.72	10	8
Antisocial	27	0.97	4.17	1.35	1.26–6.67	9	6
Borderline	26	0.94	4.64	0.99	2.27–6.38	11	8
Avoidant	26	0.94	3.98	1.18	1.42–6.31	5	3
Dependent	23	0.91	3.94	1.23	1.70–6.67	6	5
Compulsive	27	0.96	3.92	1.22	1.63–6.78	10	7
Passive-aggressive	26	0.94	4.06	0.97	2.12–6.60	5	3

[a]Each respondent was asked to rate one patient known to him or her who showed prototypical features of a specified *DSM-III* personality disorder diagnosis.

Reliability of Trait Classifications

In the first study, highly prototypical traits were printed on separate cards. Twenty clinicians were asked to classify these traits into defined dimensions for a single diagnosis. Each clinician sorted traits for five or six diagnoses. Thus, the traits of each diagnosis were sorted by 10–13 clinicians.

The clinicians' assignments of traits to dimensions were examined for agreement with the assignment I had made. The mean agreement between the 20 clinicians and myself ranged from 93.7% for borderline personality disorder to 62.3% for dependent personality disorder; the overall mean was 74.7%. Disagreement was not distributed across all traits; for 71.2% of the traits sorted into dimensions there was high agreement (defined as 75%) between the clinicians and myself. Disagreement arose primarily from two sources: 1) some traits could be appropriately classified in several dimensions, as discussed previously, and 2) clinicians differed in their interpretation of some traits. For example, "shows disregard for the consequences of his or her own actions," a trait highly prototypical of antisocial personality disorder, was classified in the impulsiveness dimension by some clinicians, while others emphasized the connotations of "disregard" and classified it in the remorselessness dimension. Such examples shed light on some of the reasons for the unreliability of personality disorder diagnoses and substantiate the need for a carefully defined lexicon of personality pathology.

Content Validity

In the second study the 79 dimensions were used to construct a 7-point rating scale that was mailed to a second sample of psychiatrists. Respondents used this scale to rate a patient known to them who, in their opinion, showed the classical or prototypical features of a specified *DSM-III* personality disorder diagnosis. Scales were arranged so that a rating of 7 represented a highly prototypical feature and a rating of 1 represented the least prototypical feature. The ratings therefore indicate the degree to which each dimension was judged to be prototypical of each diagnosis. Definitions of each dimension were provided to ensure that respondents had the same understanding of the meaning of a dimension and to minimize the effects of the connotations of the terms.

The rating scales were mailed to a random sample of 1,167 members of APA. Each psychiatrist was asked to rate a single *DSM-III* diagnosis. Responses were received from 304 (26.0%) of the psychiatrists. (Twenty-two responses relating to self-defeating personality are not described in this article.) Response rates were similar for each diagnosis (table 2). Respondents had a mean±SD age of 50±11.6 years; 252 (82.9%) were men, 30 (9.9%) were women, and 22 (7.2%) did not specify their sex.

Alpha coefficients, computed to determine the agreement among the respondents rating each diagnosis, were uniformly high, indicating agreement when dimensions were ordered from high to low prototypicality (table 2). Examination of the distribution of the mean ratings shows that for each diagnosis some dimensions were rated highly, indicating that the respondents thought the dimensions were highly prototypical features of each diagnosis.

I also examined the extent to which the respondents to this survey agreed with the 938 psychiatrists who responded to an earlier mail survey (9) as to which dimensions were the most prototypical of each diagnosis. To do this, dimensions were first ranked according to their mean prototypicality rating. For each diagnosis the measure of replication was the number of dimensions identified in the earlier survey that occurred in the highest-ranked set of dimensions in this survey; the size of the highest set was equal to the number of dimensions used to classify highly prototypical traits in the earlier survey. For example, eight

dimensions were required to categorize traits highly prototypical of schizoid personality disorder. The set of dimensions from this survey that were used to establish correspondence were those ranked in the first eight. Six of the dimensions identified in the earlier survey matched six of these eight dimensions (table 2). Agreement between the two studies ranged from eight out of 10 dimensions for narcissistic personality disorder to three of five dimensions for passive-aggressive and dependent personality disorders. The overall agreement was 77.4%. Agreement increased to 91.7% when the highest set of dimensions was defined as twice the number of dimensions identified in the earlier survey. These replication requirements are stringent in that the list of dimensions included some that were relevant to a given diagnosis even though they were not highly prototypical. For example, "reluctant self-disclosure" was not used to classify any highly prototypical schizoid traits but is often associated with schizoid personality disorder. In view of the inclusion of such relevant dimensions, agreement between the two studies was high. Thus, the dimensional definitions appear to possess satisfactory content validity.

AN ILLUSTRATIVE DEFINITION

These results may be organized by using the hierarchical structure of traits (dimensions), general habits, and specific behaviors already described. The earlier mail survey (9) had identified specific behaviors that clinicians considered highly prototypical of each diagnosis, and these may be used as diagnostic criteria. General habits were identified through a rational analysis of each dimension and by examining the traits used to define the dimension. To avoid confusion, the intermediate level of description will be referred to as a "facet." Each dimension is therefore subdivided into facets, which are subdivided into specific behavioral items. The process is illustrated in appendix 1 for schizoid personality disorder. The prototype is based on those dimensions which were replicated in this study's mail survey and hence does not include all the dimensions listed in table 1. For routine clinical use, specification to the facet level will probably be adequate, but research use will generally require specification to the item level because the reliability of an estimate of a dimension increases with the number of items on which it is based (14, 15). Specification of facets of each dimension is valuable because it contributes to convergent validity by ensuring that behaviors are selected to sample the entire domain represented by the dimension and because scrutiny of facets across dimensions provides a further conceptual review of the distinctiveness of dimensions and thus contributes to divergent validity.

Appendix 1 contains two hierarchies, the hierarchy of increasing descriptive generalization and a prototypicality gradient, since dimensions are organized from the most prototypical (low affiliation) to the least prototypical (self-absorption) dimension. The number of dimensions included in the prototype depends on the definition used to identify highly prototypical traits. A more stringent definition would have led to the inclusion of fewer dimensions in the prototype, while a more liberal definition would lead to the inclusion of more dimensions.

DISCUSSION

The approach described in this paper provides a theoretical taxonomy of personality disorder based on clinical observation and theory that provides a starting point for developing a valid classification. Instead of selecting dimensions and criteria in an arbitrary way by using implicit concepts of diagnoses, as has been done hitherto, dimensions are identified and defined systematically and explicitly in ways open to public examination, and criteria are selected to sample all facets of each dimension.

The traits of personality disturbance identified from the clinical literature can be arranged in a variety of ways because personality concepts are fuzzy and merge with each other. The dimensions were developed to define the more prototypical features of each diagnosis. The results of the sampling of clinical opinion described in this paper suggest that they successfully represent clinical concepts. The procedure involves the sequential application of the concept of content validity to establish a set of preliminary dimensions and definitions. The emphasis placed on identifying and defining dimensions that are distinct helps to ensure that convergent and divergent validity are built into the classification from the beginning (16, 17). The dimensions themselves provide a lexicon of the basic phenomena of personality pathology that will be useful quite independently of the diagnoses they define. Nevertheless, the clusters of dimensions composing an ideal type or prototypical description of each diagnosis will be useful only to the extent that they facilitate empirical studies and are supported by empirical evidence. Because the dimensional descriptions were constructed from clinical knowledge refined by sampling clinical opinion, their validity needs to be established through observations of actual patients. Evidence for a dimension will be furnished by demonstrating that the definition may be used to develop a homogeneous and distinct set of criteria. The validity of the dimensional descriptions of personality disorders will derive from empirical demonstrations in samples drawn from clinical populations that dimensions cluster as predicted and that these clusters predict clinical outcomes.

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APPENDIX 1. Brief Definitions of Dimensions, Facets, and Illustrative Behavioral Items for Diagnosis of Schizoid Personality Disorder

Dimension 1: Low affiliation—socially withdrawn, unsociable, uninterested in social activities
- *Facet 1:* Declines opportunities to socialize
  - *Behavior:* Crosses the street to avoid meeting acquaintances
  - *Behavior:* Declines invitations even when he or she has nothing else to do
- *Facet 2:* Does not initiate social contact
  - *Behavior:* Does not extend social invitations to other people
  - *Behavior:* Does not initiate conversations
- *Facet 3:* Does not participate when in a social situation
  - *Behavior:* Stays on the periphery of social groups
  - *Behavior:* Stands back and watches others rather than participating
- *Facet 4:* Has few friendships
  - *Behavior:* Has only one or two close friends, including family
  - *Behavior:* Considers relations with others to be distant

Dimension 2: Avoidant attachment—avoids intimacy, avoids close personal relationships.
- *Facet 1:* Avoids attachment relationships
  - *Behavior:* Avoids getting close to others
  - *Behavior:* Prefers not to become too involved with others
- *Facet 2:* Fearful of attachment relations
  - *Behavior:* Expresses fears about getting close to people
  - *Behavior:* Feels uncomfortable in close relationships
- *Facet 3:* Does not seek out particular others at times of stress
  - *Behavior:* Does not turn to other people when worried
  - *Behavior:* Prefers to deal with serious problems by himself or herself
- *Facet 4:* Shows little reaction to separation from or reunion with attachment figures
  - *Behavior:* Does not react when someone close returns after being away for a long time.
  - *Behavior:* Is not concerned when someone close is away

Dimension 3: Defective social skills—unsure of what to say or do in social situations, poor conversational skills
- *Facet 1:* Poor conversational skills
  - *Behavior:* Does not know what to say to people
  - *Behavior:* Has difficulty thinking of new topics of conversation
- *Facet 2:* Does not show the usual pattern of eye contact during interactions
  - *Behavior:* Avoids looking people in the eye when talking to them
  - *Behavior:* Looks anywhere other than at the person he or she is with
- *Facet 3:* Clumsy and awkward mannerisms
  - *Behavior:* Makes awkward movements and gestures when talking to someone.
  - *Behavior:* Does not know what to do with hands when involved in a conversation.

Dimension 4: Restricted affective expression—flat, unresponsive, unemotional
- *Facet 1:* Does not display affect
  - *Behavior:* Does not show feelings
  - *Behavior:* Rarely smiles
- *Facet 2:* Avoids affectively arousing situations and activities
  - *Behavior:* Stays away from emotional occasions
  - *Behavior:* Leaves situations that become emotional

Dimension 5: Social apprehensiveness—fearful and apprehensive in social situations
- *Facet 1:* Self-conscious in social situations
  - *Behavior:* Feels self-conscious with other people
  - *Behavior:* Acutely aware of everything he or she does, even when with friends
- *Facet 2:* Fearful and apprehensive in social situations
  - *Behavior:* Very uncomfortable in social situations
  - *Behavior:* Cannot relax when with friends

Dimension 6: Self-absorption—preoccupied with inner world
- *Facet 1:* Preoccupied with inner world
  - *Behavior:* Thoughts seem more real than external events
  - *Behavior:* Reports that others say he or she lives in his or her own little world
- *Facet 2:* Inattentive to things occurring around him or her
  - *Behavior:* Only half notices what is going on around him or her
  - *Behavior:* Not fully attentive to what others say
- *Facet 3:* Feels isolated from external world
  - *Behavior:* Feels cut off from what is going on around him or her
  - *Behavior:* Feels like an outsider in a group of people

Pharmaco-Epidemiology in 136 Hospitalized Schizophrenic Patients

Julie Magno Zito, Ph.D., Thomas J. Craig, M.D., M.P.H., Joseph Wanderling, M.A., and Carole Siegel, Ph.D.

The authors surveyed pharmacotherapy in a group of 136 newly admitted patients with a DSM-III *diagnosis of schizophrenia. They found that nine antipsychotic agents were used; the median daily dose (in chlorpromazine equivalents) was 1088 mg (mean±SD=1428±1260 mg; range=75–6186 mg). Women received greater mean daily doses of antipsychotics than men (1688 versus 1284 mg). Using a Cox model survival analysis, the authors found no statistical association between length of stay and the mean daily dose of antipsychotic medication. The mean daily dose of high-potency agents was 2.7 times greater than the dose of low-potency agents. The excess exposure to haloperidol alone resulted in 16.3% of the overall neuroactive drug costs.*

(Am J Psychiatry 1987; 144:778–782)

Over the past three decades, the inpatient treatment of schizophrenia has undergone dramatic changes as the result of the introduction of more specific diagnostic criteria and symptom-specific antipsychotic medication. Despite these changes, problems still exist in the appropriate use of medications, particularly in the large public institutions such as state and Veterans Administration (VA) hospitals, which serve the bulk of this patient population. Studies have failed to demonstrate a dose-response relationship (1) and have attested to the inappropriate use of medication (2). Although there has been an emphasis on achieving the lowest effective doses to minimize the risk of tardive dyskinesia (3), there is still evidence of substantial drug exposure. In addition, a 1984 study (4) provided evidence of greater exposure to high-potency antipsychotic agents than to low-potency agents. A related issue, the extent to which medication use affects length of hospital stay, is not clear. As new patient reimbursement methods such as diagnosis-related groups (DRGs) focus on length of stay, examinations of the effect that differing treatment modalities have on length of stay are required.

These issues motivated the study reported here, which is both descriptive and analytic. Drug-prescribing patterns for a group of newly admitted schizophrenic patients in a large suburban New York State psychiatric center are described in terms of what neuroactive drugs were prescribed, in what amounts, and at what costs. In addition, the hypothesis of a relationship between drug use and length of stay is tested.

METHOD

The study group consisted of all 136 admissions to Rockland Psychiatric Center in a 3-month period (September 1 through November 30, 1984) with a *DSM-III* admission diagnosis of schizophrenia. Data from a computerized information system (5) were used to describe each patient in the study group according to demographics, class of neuroactive medication ordered, daily dose of antipsychotic administered, and length of stay. The follow-up period for each patient was from 3 to 6 months, depending on the date of their admission. A patient admitted on the first day of the 3-month admission period was followed to the time of discharge or 6 months, while a patient admitted at the end of the admission period was followed for up to 3 months.

Drugs were classified into one of six American Hospital Formulary Service therapeutic classes of neuroactive drugs: 1) antipsychotics, 2) anxiolytics, sedatives, and hypnotics, 3) antidepressants, 4) anticonvulsants, 5) antimanic agents, and 6) antiparkinsonians (anticholinergics and diphenhydramine used to treat parkinsonian side effects of the antipsychotics). For antipsychotics, doses were expressed in chlorpromazine equivalents (6) and daily doses were cumulated over drug-treatment days to yield the mean total daily dose over the hospitalization period.

Statistical tests were used to compare the proportion of patients receiving a drug class by sex and for the

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antipsychotic class in terms of mean total daily dose for sex and age. The mean total daily dose of patients receiving high-potency agents was compared with that of patients receiving low- to moderate-potency agents as an expansion of the work of Baldessarini et al. (4). High-potency agents included fluphenazine, haloperidol, thiothixene, and trifluoperazine, and the low- to moderate-potency group included chlorpromazine, thioridazine, mesoridazine, molindone, and perphenazine. Because of a lack of consensus in the literature regarding the dosing conversion rule for the decanoate form of fluphenazine, the data were analyzed both with and without the inclusion of patients receiving fluphenazine decanoate. The calculation of costs for each drug ordered was based on the cost per milligram of the unit of use obtained from pharmacy purchasing information current as of October 1, 1984. This, multiplied by the product of the total mg/day and the length of time of the drug order, was the total cost of the drug order.

Two approaches were taken to examine the relationship between drug use and length of stay. In the first, the patients were divided into two groups: patients discharged within 90 days and patients hospitalized for more than 90 days. The two groups were compared on the sociodemographic variables of age, sex, ethnicity, most recent marital status, and most recent legal status. The two groups were compared for use of medications by neuroactive drug class and, for the antipsychotic class, by potency (mean total daily dose).

In the second approach the relationship between length of stay and mean total daily dose of antipsychotic was examined by using a Cox proportional hazards survival model (7). This model fits a probability distribution function to the variable length of stay (survival time), under the assumption that the conditional probability of being discharged at a particular time, given that the patient has not yet been discharged, is proportional among patients, the proportionality constant depending on the mean total daily dose. The model was developed as if all patients had 6 months of follow-up and takes into account the variability of the actual follow-up period by considering all those followed up for less than 6 months and not yet discharged as censored observations.

RESULTS

One hundred thirteen (83%) of the 136 patients were between the ages of 18 and 44 years; 73 (54%) were less than 35 years of age. The mean±SD age of the entire study group was 35.4±12.6 years. Eighty-seven (64%) were men and 65 (48%) were of black or Hispanic ethnic origin. One hundred three (76%) of the patients had never married, and 76 (56%) were admitted involuntarily.

One hundred thirty-three (98%) of the 136 patients received 919 orders for neuroactive medications. Of these, 702 (76%) were scheduled orders, 141 (15%) were for medication as needed, and 76 (8%) were for immediate one-time-only (stat) medication. Since the actual use of medications ordered to be administered as needed could not be readily obtained, only scheduled orders and orders for immediate (stat) medication were counted in subsequent analyses.

TABLE 1. Antipsychotic Medications Prescribed for 136 Newly Admitted Schizophrenic Patients During a 3–6 Month Period

Medication	Patients Receiving Medication	
	N	%[a]
Antipsychotics	129	95.0
Fluphenazine	55	40.4
Hydrochloride	34	25.0
Decanoate	44	32.4
Haloperidol	39	28.7
Chlorpromazine	24	17.6
Thiothixene	19	14.0
Thioridazine	8	5.9
Trifluoperazine	8	5.9
Mesoridazine	7	5.1
Perphenazine	7	5.1
Molindone	2	1.5
Other neuroactive drugs	4	2.9

[a]Column total exceeds 100% because patients were exposed to more than one antipsychotic.

An antipsychotic was prescribed for 129 (95%) of the 136 patients, and antiparkinsonians were prescribed for 78 (57%). Twenty (15%) of the patients received lithium carbonate, 10 (7%) received antidepressants, eight (6%) received anticonvulsants, and 24 (18%) received a medication in the anxiolytic-sedative-hypnotic group.

There were no significant sex differences in the proportion of patients receiving any of the neuroactive drug classes except for lithium, which was prescribed about three times more often for women than for men: 12 (24%) of the 49 women and eight (9%) of the 87 men were prescribed lithium.

Use of Antipsychotic Drugs

The nine antipsychotics used during the study period are listed in table 1 in the order of the number of patients given each drug. The most commonly prescribed antipsychotics in the 94 patients receiving only one antipsychotic were fluphenazine (29 patients, 31%) and haloperidol (24 patients, 26%), followed by thiothixene (12 patients, 13%) and chlorpromazine (11 patients, 12%). When two or more antipsychotics were used (35 patients), they were almost invariably used in sequence rather than in combination. Among the 32 patients receiving two antipsychotics during their hospital stay, three general patterns emerged. Sixteen (50%) of these patients were switched to fluphenazine decanoate from an oral antipsychotic. Less frequently, the switches involved a change from one high-potency agent to another (five patients, 16%) or from a more potent to a less potent antipsychotic (four patients, 13%). The remaining seven patients

received the two antipsychotics in other sequences. There was also no pattern evident for the three patients who received more than two antipsychotics.

The median chlorpromazine-equivalent dose of all antipsychotics was 1088 mg (mean±SD=1428±1260 mg; range=75–6186 mg). One hundred sixteen (90%) of the 129 patients receiving antipsychotics were treated with mean daily doses of less than 2875 mg. For 13 (10%) of the patients, daily doses ranged from 2875 to 6186 mg.

The sex-specific data indicated that the 46 women receiving antipsychotics were given greater mean daily doses (1688±1556 mg) than were the 83 men receiving antipsychotics (1284±1044 mg); this difference approached significance (t=1.75, df=127, p=.08). Age was not significantly correlated with mean total daily dose (r=−.03, N=129, p=.73), although the mean total daily dose for the 20 patients over 45 years old was about half of the daily dose for younger patients (1536 mg versus 838 mg, t=2.3, df=127, p=.03).

Excluding the 29 patients receiving fluphenazine decanoate, we found that the 54 patients who received only the oral high-potency medications had significantly greater equivalent mean daily doses (1137 mg) than did the 24 patients who received only the oral low- to moderate-potency medications (419 mg) (t=4.8, df=76, p<.0001). The 2.7 times greater exposure that we observed would have been even more inflated if the mean total daily dose (2694 mg) of the 29 patients receiving only high-potency fluphenazine decanoate had been included. The previously noted sex difference in mean total daily dose may be partially explained by the fact that a nonsignificantly higher proportion of women (87%, N=40) than men (78%, N=65) received high-potency agents.

Use of Antiparkinsonian Drugs

Benztropine was prescribed for 69 (88%) of 78 patients receiving antiparkinsonians, diphenhydramine was prescribed for 10 (13%), and trihexyphenidyl was prescribed for eight (10%). Antiparkinsonian drugs were used by 77 (60%) of the 129 patients who received antipsychotics. In the case of 44 (57%) of these patients, antiparkinsonian drugs were started at the time antipsychotic drug treatment was started, while the remainder received the antiparkinsonian some time after the antipsychotic was started.

Cost Findings

The total expenditure for neuroactive medications for the 136 patients in the study was $7,806 for 11,686 treatment days, resulting in a mean cost of $0.67 per drug treatment day.

There was considerable variation in the mean total daily dose of antipsychotic agents for the three most frequently used drugs (table 2). Despite the standard chlorpromazine-equivalent relationship of 50:1 cited for chlorpromazine to haloperidol, haloperidol was actually prescribed at twice the equivalent mean daily dose of chlorpromazine (50:2). This translates into 5.6 times the cost per day, which is twice the 2.8-fold expected differential in cost/mg if patients receiving haloperidol had been prescribed doses according to the standard chlorpromazine-equivalent dosage. If haloperidol had been prescribed in the standard chlorpromazine-equivalent dosage, patients would have received a mean of approximately 725 mg less of haloperidol per day, which in terms of total dollars would have resulted in a 16.3% saving. If one assumes that the relatively greater doses of high-potency agents were warranted, a cost saving could be realized if fluphenazine were substituted for haloperidol. Given the lower mean total daily dose of fluphenazine used in this study group and the lower cost/mg of fluphenazine relative to haloperidol, substitution of fluphenazine for haloperidol would result in a halving of cost.

TABLE 2. Average Daily Cost for the Three Antipsychotic Medications Most Often Prescribed for 129 Schizophrenic Inpatients

Medication	Cost (dollars)		Dose (mg/day)	
	Per Milligram[a]	Per Day[b]	Actual[c]	Chlorpromazine Equivalents
Chlorpromazine	0.00022	0.16	727	727
Haloperidol	0.03100	0.89	29	1450[d]
Fluphenazine hydrochloride	0.01900	0.44	24	1200[d]

[a]Averaged over units of use.
[b]Total cost of medication divided by total number of days medication was prescribed.
[c]Total milligrams of medication divided by total number of days medication was prescribed.
[d]50 × actual dose, based on relative potency of chlorpromazine to medication of 50:1.

Length of Stay and Drug Use

Seventy-one (52%) of the 136 patients were discharged within 3 months of admission; the remaining 65 (48%) patients were hospitalized for more than 90 days. In the latter group, one death and 16 discharges occurred by the end of 6 months, leaving a total of 48 patients. By using chi-square tests, these patients were compared with the 71 patients who had been discharged within 3 months. Results were nonsignificant for the two length-of-stay groups on the following variables: sex, ethnicity (white versus nonwhite), marital status (never married versus other), and legal status (voluntary versus nonvoluntary). The difference between mean ages of the two groups approached significance (t=1.75, df=134, p=.08). Seventeen (74%) of the 23 patients older than 45 years were in the group with a length of stay greater than 3 months.

There were no significant differences in the proportion of patients exposed to antipsychotics, antiparkinsonians, or lithium between the two length-of-stay groups. A greater proportion of patients in the longer-stay group received anticonvulsants and antidepres-

sants, but the numbers were too small to permit statistical testing. The proportion of patients receiving anxiolytics was not significantly different between the two length-of-stay groups, except for amobarbital, which was prescribed (on an immediate [stat] basis) only for patients in the longer-stay group. There was no significant difference between the length-of-stay groups in terms of mean total daily dose of antipsychotic.

The result of the Cox proportional hazards analysis indicated that the likelihood of being discharged was not related to the patient's mean total daily dose of antipsychotic medication, since the standardized estimate of the coefficient, beta (0.39), did not significantly differ from zero.

DISCUSSION

Previous studies of the prescribing of psychotropic drugs include cross-sectional community surveys (8), hospital- or facility-based drug use studies (9–15), and clinical epidemiologic studies using aggregate data in retrospective analyses (16–18). The valid interpretation of data from such studies requires that the analysis include relevant patient variables, such as diagnosis, age, duration of hospitalization, and severity of illness (19). The present study adds to earlier studies by presenting data on recent (1984–1985) neuroactive drug use in a group of hospitalized patients with a *DSM-III* diagnosis of schizophrenia using a longitudinal design that allowed us to follow the medication changes from admission through a 3–6-month period.

Data on the pharmacotherapy of this recently admitted group of schizophrenic patients confirms the central role of antipsychotic drugs as the mainstay of therapy in the hospitalized patient. A study conducted in this hospital in 1968 by Laska et al. (10) found that 88% of all schizophrenic patients received a neuroactive medication and that 97% of these medications were in the antipsychotic class. In our study, however, we found that virtually all (98%) of a newly admitted group received medications and that 95% of these medications were in the antipsychotic class. Comparison with the findings of Craig and Behar (11) on the relative frequency of antipsychotic classes supports a shift away from the use of low-potency agents and newer classes of antipsychotic drugs such as indoles and dibenzoxazepines toward higher-potency groups. Whereas the piperidine phenothiazines accounted for nearly 30% of the drugs given patients in 1970 (11), we found that only 16 (12%) of our group of patients received them in 1984. Butyrophenone use rose from 9% in 1970 to 30% (N=41) in 1984, and use of piperazine derivatives, mainly fluphenazine, rose from 35% to 52% (N=71) during the same period. This trend toward increased piperazine use is almost entirely explained by the increased popularity of the long-acting decanoate form.

Patients who were given only high-potency agents tended to receive a 2.7-fold greater exposure to the drugs than patients receiving only low- to moderate-potency antipsychotics, as measured by average daily chlorpromazine-equivalent milligram doses. This finding is consistent with the findings of Baldessarini et al. (4) in a 1984 survey of community and VA hospitals. A possible explanation for this observation is the relatively greater severity of illness of patients who receive high-potency agents. To explore this issue, we looked at a subset of 66 patients for whom data were available on previous hospitalizations at our facility. We assumed that greater chronicity was indicative of greater severity of illness. Forty-four (66%) of these patients had one or more previous inpatient admissions. Contrary to our expectation, patients who received high-potency agents did not have a significantly greater number of previous hospitalizations, nor did they have a significantly greater number of previous inpatient days (analysis of variance).

A more compelling argument for the relatively greater exposure to high-potency agents is the difference in side effect profiles of the two drug groups, which may allow a greater tolerance for high doses of high-potency agents. Low-potency agents produce more sedation and hypotension, which are debilitating and readily observable effects, whereas the extrapyramidal effects of the high-potency agents until recently were often difficult to distinguish from new symptoms of illness.

The absence of a significant relationship between chlorpromazine-equivalent dose of antipsychotic drugs and length of stay found in this study underscores the need for future studies to clarify antipsychotic dose-response relationships in humans. There are several possible alternative explanations for the lack of an observed relationship in these data. For example, the heterogeneity of the patient population may produce subgroups whose dose-response characteristics are not reflected by average data.

Nevertheless, the wide range of mean total daily doses among the nine antipsychotics (75–6200 mg) suggests a great variation in prescribing patterns. These differences persist despite the claim of most experts that the efficacy of doses greater than 1800 mg/day for acutely ill schizophrenic patients (20) and 900 mg/day for the management of chronic schizophrenia have not been substantiated by empirical studies or meta-analysis (3). The present data do not directly support the underlying assumption of many prescribing decisions—that rapid, enhanced dosing will shorten the patient's stay. Rather, these data provide an empirical basis for more rigorous study of low-dose regimens without fear that such approaches would necessarily produce longer stays, particularly in chronic patients (21).

The present findings of a marked discrepancy in mean daily chlorpromazine-equivalent doses between low- and high-potency antipsychotic agents in the absence of an association between the dose level and length of stay suggests the need for a reassessment of

the currently used conversion formulas for antipsychotic drug equivalence. In particular, there is a need for rigorous empirical studies to establish valid conversion rules in regard to depot forms of fluphenazine and its newly developed competitor, haloperidol. Double-blind prospective studies are needed to ascertain an oral-to-depot conversion dosing rule and to provide serum-level–dose-response correlations (22). In the absence of such studies, the present data suggest that a substantial proportion of hospitalized schizophrenic patients are exposed to chlorpromazine-equivalent doses which are clearly in excess of current guidelines and may contribute to an unrecognized behavioral toxicity. In particular, fully 10% of the patients received chlorpromazine-equivalent doses of antipsychotic in excess of 2.5 g/day.

This study has shown that medicating the hospitalized schizophrenic patient is inexpensive ($0.67 per drug treatment day) despite the relatively large daily doses used. Nevertheless, in the light of the relatively greater exposure to high-potency agents, further reductions in cost might be achieved without loss of clinical quality if switches from higher-priced agents to clinically similar alternatives were made.

Relatively few changes in antipsychotic medication were made over the course of an episode. The changes most often seen were generally appropriate and consisted of changes from short-acting oral to long-acting injectable forms or from low-potency to high-potency agents, reflecting concerns for outpatient regimens to maximize compliance. However, of concern was the general absence of any trend toward reduced doses over time during a switch from acute treatment to maintenance, when reductions might be expected. Eclectic drug therapy was more frequent among longer-stay (91 days or more) patients. Trials of antidepressants, lithium, and anticonvulsants (e.g., carbamazepine for unlabeled use) occurred in about 20% of the patients who failed to achieve discharge within 90 days. If extended stay can be attributed to the equivocal response to antipsychotic drug treatment among these schizophrenic patients, a question can be raised about whether a trial of an alternative medication such as propranolol or carbamazepine might have been useful in a greater proportion of patients. Efforts to systematically evaluate the use of medications for such unlabeled indications are needed. Eight (40%) of the 20 patients who received lithium had diagnostic changes that explained the use of lithium. Four patients had a change of diagnosis to bipolar affective disorder during this admission, and four had a past history of this diagnosis. Immediate (stat) amobarbital use, suggestive of unstable drug management, occurred exclusively in longer-stay patients and is consistent with the greater difficulty in managing patients who fail to attain discharge within 90 days.

The design of this study does not permit inferences of a causal nature. However, the findings do raise questions in an epidemiologic context. The challenge is to identify behavioral toxicity and the drug combinations or dose range of single antipsychotic agents in which these symptoms are most likely to occur. One of biological psychiatry's greatest challenges today is the need to discriminate drug-induced behavioral toxicity from illness behaviors.

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Editorial

Long-Term Perspectives on Persons With Chronic Mental Disorder

Detailed knowledge about the clinical course of major psychiatric disorders is extremely important if effective interventions are to be designed and implemented, but research to develop this essential information is exceedingly rare. The two articles by Courtenay Harding, George Brooks, Takamaru Ashikaga, John Strauss, and Alan Breier in this issue of the *Journal* add substantially to knowledge in this area.

Harding and colleagues report findings from a 20- to 25-year follow-up study of a cohort of 269 patients discharged between 1955 and 1960 from Vermont State Hospital to a comprehensive rehabilitation and community placement program. As originally reported in *The Vermont Story* (1), the prognosis of these patients was uniformly poor. All suffered from severe and persistent mental disorders, as reflected through diagnosis, duration of illness, level of disability, and history of inpatient care. Although an earlier follow-up study found that 70% of the cohort was residing in the community 5–10 years after the date of the index discharge, the prognosis was that lifetime care would be required. In this context, the findings reported by Harding and colleagues are of great interest. They found that between one-half and two-thirds of these patients had improved considerably or recovered 20–25 years after the index discharge.

To discount the hypothesis that the patients' disorders had been misdiagnosed, Harding and colleagues made clinical reappraisals of the original primary case records and abstracts with *DSM-III* criteria. Of the original 213 patients given a diagnosis of schizophrenia according to *DSM-I* criteria, 114, or 54%, retained the same diagnosis when *DSM-III* criteria were used, and four new cases were added. With very few exceptions, living members of this group participated in the long-term follow-up study. Results were essentially identical to those for the larger cohort. Harding and colleagues found that one-half to two-thirds of those with a retrospective *DSM-III* diagnosis of schizophrenia had achieved considerable improvement or recovery.

This long-term follow-up study has several clear implications for the field. Since Harding and colleagues found that persons with serious and persistent mental disorders experience a variety of long-term outcomes, research on factors that influence outcome is a high priority. Diagnosis was not found to be an accurate predictor. Hence, current diagnostic formulations need to be re-examined, and other factors that may influence outcome require investigation. The latter include psychosocial and vocational functioning before and after the onset of the disorder, as well as the effects of treatment and system interventions, among others. Finally, this research demonstrates both the feasibility and the importance of long-term research on the course of major psychiatric disorders. To date, very few longitudinal studies have been conducted in the United States.

To better understand the effects of the Vermont rehabilitation program, Michael DeSisto and colleagues are developing comparative retrospective and follow-up information on a cohort of patients from Augusta Mental Health Institute in Maine who have been matched to the Vermont subjects on sociodemographic and clinical variables. Persons from the Maine cohort will be studied with the same follow-up battery as the one described by Harding and colleagues. This research will add

appreciably to our knowledge about the clinical course of major psychiatric disorders and will help us to understand the effects of the Vermont rehabilitation program, since persons in the Maine cohort did not receive such treatment.

Improved understanding of the major mental disorders is a very high priority. The staggering human, familial, community, and financial costs of these illnesses are well known and do not require restatement here. What must be addressed are the types of research that will facilitate development of the knowledge we need.

The research conducted by Harding and colleagues, and by their predecessors more than a quarter of a century ago, is essentially naturalistic. When undertaken at all, this kind of research is likely to result from a demonstration program of the type portrayed in *The Vermont Story*. We need more research of this type to examine the clinical course of major psychiatric disorders from onset until recovery or death. Such research is extremely difficult for obvious reasons (e.g., inability to locate persons in the cohort) and for less obvious reasons (e.g., the research may extend beyond the professional lifetimes of the investigators, and the "payoff" to researchers engaged in such research may preclude tenure, publications, etc.). Similarly, the development of good record-keeping systems, a perennial problem, is fundamental in the earliest stages of the research. In the work by Harding and colleagues, reappraisal with *DSM-III* criteria would have been impossible without such records.

Specification of the long-term effects of pertinent interventions is as important as understanding the course of disease. The introduction of longitudinal data on a matched comparison group, as is currently being done by DeSisto and colleagues in Maine, will permit some assessment of the effects of the Vermont rehabilitation program through a quasi-experimental design. As with the research by Harding and colleagues, the research currently underway is based partially on retrospective data, with the requirement of high-quality record systems.

Although prospective clinical trials with randomized case assignment are critical for understanding the effects of specific psychiatric treatments, most persons with severe and persistent mental disorders simultaneously require these treatments *and* other mental health, medical, and social services. The historic Vermont rehabilitation program and the current Robert Wood Johnson Foundation Program for the Chronically Mentally Ill are examples of the best efforts to improve service systems. To understand the complex effects of these care systems, research designs should be the best possible, but the inability to construct fully randomized, prospective, experimental designs in specific instances must not deter the development of essential knowledge. Matching of subjects and statistical technology are powerful tools in quasi-experimental and naturalistic contexts.

Knowledge is gained in small increments, frequently with great difficulty and in unplanned ways. As a field, we need to make a strong commitment to long-term research on the major mental disorders and the service systems designed for persons with these illnesses. Such research will amplify the pioneering efforts of Harding and colleagues. Only by starting now will we set the stage for intervening successfully and preventing these disorders in the future.

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Trazodone in the Treatment of Panic Disorder and Agoraphobia With Panic Attacks

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Kathleen Bowler, R.N., M.S.N., and Robert Dealy, M.D

Eleven patients with panic disorder or agoraphobia with panic attacks completed an 8-week single-blind trial of trazodone (300 mg/day) without concurrent behavioral instructions. The measures of change included ratings of generalized and panic anxiety, phobias, and depression and a behavioral avoidance test, which were administered during a baseline period of placebo administration and at 4 and 8 weeks of the trial. There was significant improvement on all symptom dimensions, which suggests that trazodone may have specific antipanic and antiphobic actions and underscores the importance of serotonergic mechanisms in these anxiety disorders.

(Am J Psychiatry 1987; 144:785–787)

Trazodone is a triazolopyridine derivative with antidepressant activity comparable to that of imipramine and other tricyclics in overall therapeutic efficacy and with fewer anticholinergic side effects (1). Trazodone has been found to selectively inhibit 5-hydroxytryptamine (5-HT) uptake in rat brain and platelets. Although its effects on 5-HT are moderately potent, it also has an affinity for α_1-adrenergic receptors of human brain (2). One of its minor metabolites, M-chlorophenylpiperazine, has recently been shown to be both a 5-HT uptake inhibitor and a potent direct agonist of postsynaptic 5-HT receptors. Although the amount of this metabolite is small, its transport into the CNS appears to be greater than that of trazodone, and there is a possibility that it is biochemically active. This duality of functions, i.e., as reuptake inhibitor and receptor agonist, would make trazodone significantly serotonergic at normal therapeutic doses (3).

Several clinical reports have suggested that the drug may have anxiolytic effects in depressed and, more important, primarily anxious populations. Wheatley (4) found that trazodone and chlordiazepoxide were equally effective in relieving anxiety symptoms in 83 general practice patients, the majority of whom were diagnosed as having anxiety neurosis. Another double-blind randomized comparative study with 99 psychiatric outpatients diagnosed as neurotic "with prominent symptoms of anxiety" (5) found that during the 4-week trial diazepam and trazodone were equally effective and significantly superior to placebo in reducing scores on the Hamilton Rating Scale for Anxiety. In this paper we present data from a pilot study of trazodone for patients with *DSM-III* diagnoses of panic disorder or agoraphobia with panic attacks. No existing trial of trazodone has, to our knowledge, extended the investigation of this drug's anxiolytic effects to these reliably diagnosed conditions, which respond to imipramine or MAO inhibitors. On the other hand, bupropion, which is an effective antidepressant possessing moderate dopaminergic activity but weak serotonergic and noradrenergic effects, has been found ineffective in the treatment of patients with panic disorder or agoraphobia with panic attacks (6).

METHOD

The subjects of this study were 11 outpatients with *DSM-III* diagnoses of panic disorder or agoraphobia

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Supported by grants MH-40141 and MH-34177 from NIMH.
The authors thank Mary Sue Hamann, M.S., for assistance with the statistical analyses and Mead Johnson/Bristol-Myers for supplying the drugs.

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TABLE 1. Outcome Scores During 8-Week Trial of Trazodone in 11 Patients With Panic Disorder or Agoraphobia With Panic Attacks

Measure	Placebo Baseline		4 Weeks		8 Weeks		ANOVA Time Effects	
	Mean	SD	Mean	SD	Mean	SD	F(df=2, 20)	p
Phobia								
Fear Questionnaire								
Agoraphobia score	16.9	7.4	9.5	4.9	7.3	4.5	29.21	≤.01
Social phobia score	13.9	8.1	10.8	7.4	8.6	7.1	12.30	≤.01
Blood-injury score	11.5	4.9	7.9	5.3	6.0	3.5	9.99	≤.01
Phobic anxiety/avoidance score	5.0	1.2	3.4	1.4	3.2	1.5	14.55	≤.01
In vivo phobic anxiety/avoidance score	2.2	1.3	1.0	0.9	1.3	1.4	8.68	≤.01
Panic								
Severity score	4.4	1.0	4.5	2.1	3.1	1.5	3.70	≤.05
Number of symptoms endorsed	9.1	2.5	7.9	2.0	7.9	2.4	1.18	n.s.
Sum of symptom scores	31.5	14.6	29.5	15.2	22.7	9.0	1.89	n.s.
Number of attacks (from diary)	6.3	5.2	3.9	4.0	2.3	3.0	5.83	≤.01
Hamilton anxiety score	17.5	4.5	17.3	5.2	13.6	4.4	5.74	≤.01
Beck depression score	12.3	7.1	10.5	6.5	8.1	8.0	6.12	≤.01

with panic attacks who gave written consent and completed a single-blind trial of 8 weeks of trazodone treatment following a 2-week baseline period of placebo administration. Of nine additional patients who started the trial, two were noncompliant with the protocol requirements, two dropped out during the placebo baseline period, and five dropped out within the first 2 weeks of trazodone treatment because of increased anxiety symptoms (N=3), drowsiness (N=1), or relative leukopenia (N=1). There were no statistically significant differences in demographic or clinical variables or in pretreatment symptom severity between the patients who dropped out and the 11 who completed the trial. The latter had a mean±SD age of 34.3±8.8 years and a duration of illness of 6.1±5.8 years. Eight were female and three were male. They were all medically healthy and free of psychotropic drugs and alcohol. Only one patient met the criteria for concurrent major depressive episode.

Throughout the trial the patients were given consecutively dated vials prepared by the hospital pharmacist, each containing six identical-looking pills (composed of either placebo or 50 mg of trazodone) to be taken at bedtime. At each visit the patients returned all vials and a new set was provided. The initial dose was 50 mg/day, which was increased by 50-mg increments every 3 days until all the placebo pills were replaced with the active drug (300 mg/day). The doses of two patients had to be decreased to 200 mg/day because of extreme drowsiness and hand tremors, respectively. The patients were told that they would receive an "antidepressant" medication such as desipramine or trazodone but that this drug, unlike imipramine and monoamine oxidase inhibitors, was not an established treatment for panic disorder and agoraphobia. No instructions or encouragement for self-directed exposure to phobic situations or other coping strategies were given during the trial. The treatment was free.

Assessments were made during the placebo baseline period and at 4 and 8 weeks of trazodone treatment. These included the Hamilton Rating Scale for Anxiety, the Beck Depression Inventory, and the Fear Questionnaire (7). Panic attacks were assessed with a self-rating questionnaire adapted from the *DSM-III* criteria for panic disorder. First, the patients were asked to rate the overall severity of the panic attacks they had experienced within the last 2 weeks on a 0–8 analogue scale (0=none, 2=mild, 4=moderate, 6=severe, 8=very severe). Next, using the same scale the patients rated the severity of the 12 specific panic symptoms listed in *DSM-III;* from these ratings the number of panic symptoms endorsed and the sum of the panic scores were derived. The patients also kept a diary of the panic attacks they experienced during the 2-week placebo baseline period and again during weeks 3–4 and 7–8 of trazodone treatment. Phobic anxiety and avoidance were assessed by calculating the mean rating of each patient's five most feared situations on a 0–8 scale. Finally, the patients were asked to walk unaccompanied from the hospital into a crowded urban center and 1) to cross a wide and congested avenue, 2) to enter a large store and make a purchase, and 3) to enter a fast-food restaurant and remain there for at least 15 minutes to eat or drink. They were required to rate the level of anxiety/discomfort experienced during each of these tasks on a 0–8 scale. Incomplete tasks were assigned the maximum value of 8 and were averaged with the ratings for the completed tasks to obtain a functional in vivo measure of phobic avoidance and anxiety.

We also evaluated six patients who had agoraphobia with panic attacks and had been given placebo for 8 weeks under similar treatment conditions. They were assessed with the same instruments on the same schedule. These patients were not treated concurrently with the trazodone-treated patients. The purpose of their inclusion here is to reflect the temporal stability of symptom severity in this particular clinical population.

RESULTS

Table 1 presents the mean±SD values for the dependent measures at pretreatment and after 4 weeks

and 8 weeks of trazodone treatment. As can be seen, statistically significant improvement occurred in all symptom dimensions over the course of treatment (according to repeated measures analysis of variance). Similar analysis conducted with the placebo patients revealed statistically significant changes only on the agoraphobia scale (pretreatment: 24.7±12.5; week 4: 21.3±10.7; week 8: 17.3±9.5; $F=5.03$, $df=2, 10$, $p \leq .05$). On this scale the placebo patients improved 30% (57% in the trazodone patients) and as a group remained in the dysfunctional range (7). None of the other phobic measures, anxiety measures, or panic measures for the placebo patients showed significant improvement between pretreatment and posttreatment (social phobia score: 14.8±5.8 to 13.8±6.1; in vivo measure of phobic anxiety/avoidance: 5.0±3.9 to 4.2±3.8; Hamilton anxiety score: 19.0±4.2 to 17.2±4.4; panic severity score: 5.2±2.2 to 5.7±1.4; sum of panic symptom scores: 34.2±17.0 to 39.0±17.4).

DISCUSSION

In our study trazodone significantly reduced anxiety, panic, and phobic symptoms in psychiatric outpatients with panic disorder or agoraphobia with panic attacks. Furthermore, the care taken to eliminate the specific confounding of behavioral-cognitive instructions, the nonspecific treatment response during the first 2 weeks of the trial, and the observation that placebo treatment of patients with similar diagnoses under similar clinical and assessment conditions did not result in significant improvement suggest that the improvements noted were specific pharmacologic effects. In addition, the present findings reinforce previous reports suggesting a central rôle of serotonergic mechanisms in the treatment of panic/agoraphobia (8). A placebo-controlled trial of trazodone and imipramine for these patients thus seems warranted. This would not only enable direct comparison of trazodone's effects with the current standard pharmacotherapy of panic/agoraphobia but also would allow interpretation of the findings in light of the drugs' different pharmacologic effects on the noradrenergic and serotonergic systems.

In general, trazodone was well tolerated by these patients, who, as expected, did not complain of anticholinergic side effects. Sedation interfered with treatment in one patient but was easily remedied by dose reduction in another. Of clinical importance, three patients (19%) dropped out of the trial because of exacerbation of anxiety symptoms: primarily hot and cold flashes and heart palpitations in the first patient; dizziness, shaking, and shortness of breath in the second; and tachycardia and dizziness in the third. Although this side effect rate is similar to the 20% rate of hypersensitivity to imipramine shown by agoraphobic patients (9), the increased jitteriness, irritability, and insomnia associated with imipramine were not observed with trazodone.

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Reduction of CO_2-Induced Anxiety in Patients With Panic Attacks After Repeated CO_2 Exposure

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The authors compared the subjective reaction of 13 panic patients and eight control subjects to a 35% CO_2 challenge, a treatment known to produce physical symptoms comparable to those of natural or lactate-induced panic, and to placebo treatment (inhalation of air). They found that patients had higher placebo scores than control subjects, patients tended to get highly anxious on CO_2 and control subjects did not, and CO_2-induced subjective anxiety in patients decreased as the number of CO_2-induced exposures to interoceptive anxiety symptoms increased. The data support a behavioral account of the effects of anxiogenics.

(Am J Psychiatry 1987; 144:788–791)

The use of pharmacological models in general and the sodium DL-lactate model in particular to study nonsituational panic has recently attracted a great deal of attention. Lactate infusion induces physical symptoms that closely resemble those of natural panic attacks. Furthermore, it induces a high level of subjective anxiety in a majority of panic patients but only in a small minority of normal subjects (1, 2). The intriguing question of how lactate infusion produces its effects cannot yet be fully answered (1, 3); however, an understanding of both lactate-induced and natural panic may be gained by studying other well-defined interventions that produce comparable effects. Inhalation of carbon dioxide seems to be one such intervention.

In 20 normal subjects, a single vital capacity inhalation of 35% CO_2 and 65% O_2 reliably resulted in *DSM-III* defined neurovegetative concomitants of panic (4). One placebo-controlled study of 12 panic patients and 11 normal control subjects found that a 35% CO_2 and 65% O_2 inhalation had a clear anxiogenic effect on panic patients but hardly affected the subjective state of the control subjects (5). Comparable results were obtained in a study that used a 5% CO_2 challenge (6).

The first aim of the present study was to replicate the observation that panic patients react to a 35% CO_2 challenge with much more anxiety than do normal subjects. The second aim concerned the mechanism by which CO_2 and lactate exert their panicogenic effects.

It has been argued that panic patients suffer from metabolic disturbances in acid-base regulation and that these pathophysiological mechanisms are triggered by lactate and CO_2 challenges (6, 7). Other researchers have pointed out that while biological predisposition may play a role in the genesis and maintenance of panic, panic patients typically fear bodily concomitants of arousal (8–10).

It appears that interoceptive fears of bodily anxiety sensations may, in fact, be sufficient to explain the apparent panicogenic properties of lactate and CO_2. In other words, CO_2 inhalation and lactate infusion may produce high subjective anxiety in panic patients because they expose patients to an interoceptive phobic cue. If one assumes this is true and considers the fact that repeated and prolonged exposure in vivo to external phobic cues diminishes phobic anxiety (11–13), one may expect that the panicogenic power of CO_2 inhalation and lactate infusion will diminish if the intervention is repeated.

A group of thirteen panic patients, a control group of eight normal volunteers, and an air-inhalation placebo treatment were used to test two hypotheses: 1) that panic patients report more subjective anxiety after 35% CO_2 inhalation than do normal subjects and 2) that CO_2-induced subjective anxiety in patients drops when the intervention is repeated.

METHOD

Thirteen patients met *DSM-III* criteria either for agoraphobia with panic attacks (one man, four women) or for panic disorder (five men, three women). All

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Supported in part by grant 560-268-001 from the Dutch Organization for Fundamental Research (ZWO/Psychon).

The authors thank Riet Gierlings and François Willems for help in carrying out this experiment and Jan van Houtem for computational assistance.

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patients suffered from regular panic attacks. The mean±SD duration of patient complaints was 59±45 months, and the patients ranged in age from 20 to 42 years (mean=33.8). Eight normal control subjects (two men, six women) ranged in age from 18 to 24 years (mean=20); none had previously suffered from panic attacks or had any other psychiatric complaints. The control subjects were volunteers from a population of university students. The patients as well as the control subjects were medically examined to exclude any who might have some physical disability.

Inhalation of air was used as a placebo treatment. The subjects knew that different gas mixtures would be given on different occasions, but they did not know the type of mixture (35% CO_2 and 65% O_2 or air) or the time at which the two mixtures would be given. Although a double-blind technique was used in the treatment, the fact that the effects of CO_2 inhalation can often be observed did not escape the experimenters, who could, at best, make some educated guesses as to which gas had been administered when.

Each subject participated in nine 1-hour sessions. During each session, 10 to 12 inhalations were taken. Each subject received CO_2 during six sessions and air during three sessions. The subjects were randomly assigned to one of two inhalation sequences. Sequence 1 consisted of three sessions of CO_2, followed by three sessions of air, followed by three sessions of CO_2. Sequence 2 was three sessions of air, followed by three sessions of CO_2, followed by three sessions of CO_2. The sessions were spaced a day or two apart. Most three-session blocks were given in 1 week.

Both patients and normal subjects were told that the gas to be given was harmless, that it reproduced physical symptoms of excitement or anxiety, and that they might (or might not) experience some degree of subjective anxiety. The patients were told that repeated exposure to vegetative panic symptoms could improve their condition, and the normal subjects were told that panic symptom provocation is a therapeutic procedure to improve the condition of a subgroup of psychiatric patients by eliciting autonomic panic symptoms.

The inhalation procedure basically consisted of emptying the lungs as much as possible and then taking a vital capacity of the mixture. As early as the first session, an attempt was made to maximize the impact of the inhalation by instructing the subject to 1) take a maximum inhalation and hold it in as long as could be tolerated, 2) take double or triple inhalations (emptying the lungs, filling them with the mixture, holding their breath as long as possible, exhaling, inhaling a new full breath of the mixture, etc.), 3) inhale the mixture in a standing rather than a sitting position, and 4) administer the inhalation to themselves when the experimenter was not in the room. After each inhalation (single, double, or triple), the subjects noted on a piece of paper the level of anxiety they felt immediately after exhalation. The gas to be inhaled consisted of either a mixture of 35% CO_2 and 65% O_2 or air. A modified Entonox self-administration analgesia mask, equipped with a demand valve, was used for inhalation.

An impression of the subjective experience after inhalation was obtained by asking the subjects to rate their anxiety on a 100-point scale (0="no anxiety" and 100="the worst anxiety I can imagine") (14). The mean score from the 10–12 inhalations was taken as the subject's score for a given session.

Two separate analyses of variance (ANOVA) with repeated measures were performed on the data. The first analysis was performed to test whether panic patients react differently to CO_2 challenge than do normal subjects. It included two grouping factors—subjects (patients versus normal subjects) and sequence (CO_2 first versus air first)—and one within-subjects factor—gas (first CO_2 session versus first air session). The second analysis involved possible CO_2 exposure effects; it also included the same two grouping factors plus one within-subjects factor (all six CO_2 sessions).

RESULTS

To test the first hypothesis, we compared the anxiety scores of the patients with those of the normal subjects during the CO_2 sessions and during the air sessions (figure 1). After both air and CO_2 inhalation, the patients reported significantly higher scores than did the normal subjects ($F=16.65$, $df=1, 18$, $p<.001$). The subjects reported higher scores after CO_2 inhalation than after inhalation of air ($F=30.25$, $df=1, 18$, $p<.001$). When the difference scores (CO_2 minus air) between the patients and the normal subjects were compared, only a marginal difference emerged ($F=3.10$, $df=1, 18$, $p<.10$), probably because of one control subject who did not react to air inhalation but who became highly anxious after the first CO_2 inhalations (upper line, far right, figure 1). In the next CO_2 sessions, no more high anxiety was elicited in this subject. To further explore the first hypothesis, we included the first three CO_2 sessions, from both sequences, and the three air sessions; for each patient and each control subject, three mean difference scores were calculated. Patients had significantly higher CO_2 minus air difference scores ($F=9.96$, $df=1, 18$, $p<.006$), indicating that they were more affected by the CO_2 challenge than were the control subjects. No significant sequence effects (CO_2 first versus air first) were detected.

Because there was no significant positive (parametric or nonparametric) correlation between age and the difference score (CO_2 minus air) in either the patient or control group, the observed difference between patients and control subjects should not be attributed to discrepancies in mean ages.

To test the second hypothesis, the anxiety scores during the six CO_2 sessions were compared. The data on reduction of CO_2-induced anxiety are illustrated in figure 2. The effect of repeated exposure on the pa-

Figure 1. Subjective Anxiety of 13 Panic Patients and Eight Normal Subjects During a First Session of CO_2 or Placebo Inhalation

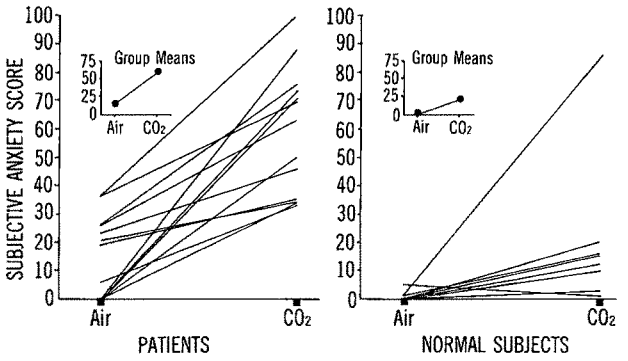
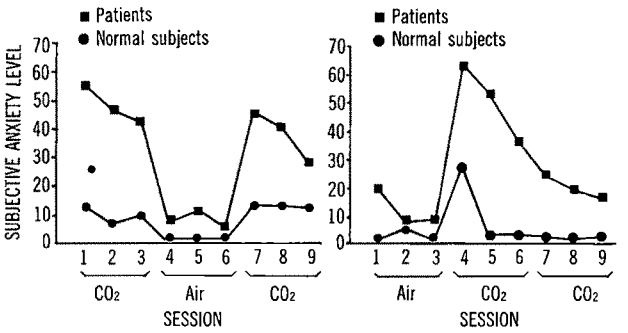


Figure 2. Reduction in CO_2-Induced Subjective Anxiety in 13 Panic Patients



tients and the normal subjects is clearly different ($F=15.75$, $df=1, 18$, $p<.001$), i.e., the patients became less anxious after repeated exposure to CO_2 challenge (reflected in their scores—$F=7.17$, $df=5, 90$, $p<.0001$—which become significantly reduced with each session) and normal subjects did not. This effect is mainly attributable to the difference in the anxiety scores of the patients (Subject by Session interaction; $F=3.28$, $df=5, 90$, $p<.01$). Again, no sequence effects were noted.

DISCUSSION

This study provides evidence that 1) panic patients experience considerably more anxiety after a 35% CO_2 inhalation than do control subjects and 2) the anxiogenic CO_2 effect diminishes as the amount of CO_2 exposure increases. With respect to the specificity of CO_2-induced anxiety to panic patients rather than to normal subjects, the patients also scored higher than the control subjects during placebo trials. This finding apparently reflects a high level of background anxiety. The fact that patients had still higher CO_2 minus air scores is not what one would expect from the law of initial values and therefore suggests, a fortiori, that CO_2 affected patients more than it did normal subjects.

Did patients panic? If the *DSM-III* definition of panic as a discrete period of apprehension or fear with at least four physical symptoms present is applied, one would have to say that all thirteen patients did, in fact, panic. Any human subject taking a deep inhalation of a 35% CO_2 mixture is bound to experience several physical panic symptoms (4). The use of such a loose *DSM-III* criterion would imply that all of the normal subjects had panicked, too—a rather unlikely event.

A stricter and more plausible criterion for panic might be four physical symptoms plus a high level of subjective anxiety. How to define "high level" and where to set its lower limit in terms of a score would be somewhat arbitrary. If a first session average CO_2 score of 50 or more is taken as the cutoff point, seven of the 13 patients and one of the eight control subjects would have met the criterion for panic. Yet patients also had higher placebo scores than did control subjects, and it has been argued (15) that if patients' higher placebo or baseline scores are taken into account, the patient-control difference between lactate and CO_2 challenge disappears. This objection does not, however, apply to our data. If a first session CO_2 score minus a first session air score of 20 or more is found, it then follows that 12 of the 13 patients, compared to one of the eight control subjects, had panicked.

Further evidence of the anxiomimetic nature of CO_2 inhalation comes from Griez et al. (5), whose patients reported a close similarity between the CO_2-induced state and clinical panic attacks. They also found a difference between patients and control subjects in psychomotor and verbal behavior, the patients typically becoming restless, putting their hands on their chests or heads, shaking their heads, moaning, crying, wanting to run, commenting on symptoms, and/or becoming flushed.

The anxiety reduction we observed in patients may be explained if one accepts the idea that panic patients suffer from an interoceptive fear of sensations that are reproduced by lactate and CO_2. This interoceptive fear apparently habituates over the course of exposure. The initial difference between patients and control subjects is compatible with a "fear-of-fear" model (16). The interoceptive fear of panic patients may constitute a strong maintaining mechanism. With regard to cause, however, fear-of-fear models may have less to offer. In cases where interoceptive fear is seen as a consequence of panic experiences (8), the occurrence of the first clinical panic attacks is left unexplained. In the present study, although patients had experienced approximately 60 CO_2 challenges, their final average anxiety level never dropped to that of normal control subjects. Would, as the slope of the curves suggest, a further reduction of anxiety have taken place if more inhalations had been given, or would the patients have reached a biological boundary of unlearning? Biological predispositions, like abnormalities in chemoregulatory CO_2 sensitivity, may play a role in the genesis and maintenance of the disorder (6, 17, 18). Such biological peculiarities may interact with learning pro-

cesses and facilitate acquisition and/or inhibit extinction of interoceptive and agoraphobic fears.

To investigate the explanatory power of fear-of-fear models, the use of lactate in a replication of this experiment would be worthwhile. Cross-validating the findings by showing that lactate vulnerability diminishes after extended CO_2 exposure or that CO_2-induced anxiety decreases after a long series of lactate infusions would also be beneficial. Particularly relevant would be an investigation into a physiological basis for the exposure/habituation effect that we observed. Would ventilatory urge and chemoreceptor reactivity change over the course of repeated CO_2 exposure?

The mode of action of CO_2 and lactate may further be clarified by comparing successfully treated patients with untreated patients. Tricyclics reduce the panicogenic power of lactate (19). Would lactate or CO_2 vulnerability also wane after successful behavioral interventions? The case history of a psychologically treated agoraphobic patient who lost her lactate vulnerability (20) should be replicated in controlled trials.

A procedural inference from our observations may be that experimenters should be cautious in using experiments with repeated measures, since habituation effects may obscure anxiogenic properties of interventions. On a clinical level, this methodological problem may be highly relevant. The adaptation to CO_2-O_2-produced or lactate-produced sensations may generalize. In fact, Bonn et al. (21) observed clinical improvement in 33 patients with anxiety neurosis treated in an open trial of six lactate sessions. A recent crossover study with propranolol-induced avoidance of interoceptions versus CO_2-induced exposure (22) demonstrated that CO_2 was superior on most measures, had a specific and strong effect on the "fear of autonomic sensations," and reduced the frequency of clinical panic attacks by 50%, observations that have also been reported in several case histories (23, 24).

Panic disorder is a complex clinical phenomenon, and there is little reason to draw overly optimistic therapeutic conclusions from small-scale incidental observations. There is, however, good reason to investigate the possibility of anxiogenics being anxiolytic.

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Treatment of Hyperactive Children With D-Phenylalanine

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Eleven hyperactive boys were treated for 2 weeks with D-phenylalanine (20 mg/kg per day) and for 2 weeks with placebo in a double-blind crossover study. Tests included parent and teacher behavior ratings, cognitive measures, and blood and urine measures of norepinephrine, amino acids, and trace amines. No significant improvement or deterioration in behavior and no side effects were noted, and only serum phenylalanine was increased by the active treatment phase. This provides reassurance about the toxicity of aspartame, a food additive that contains phenylalanine, but argues against precursor loading treatment of hyperactivity.

(Am J Psychiatry 1987; 144:792–794)

The involvement of catecholamines in the pathogenesis of attention deficit disorder with hyperactivity has been considered since Kornetsky (1) first hypothesized "an overactive noradrenergic system." Since that time a large number of pharmacological studies have tested various catecholamine hypotheses, with a confusing array of results. Our most recent work with monoamine oxidase inhibitors (2, 3) supports the hypothesis that changes in catecholamines are important in achieving therapeutic effects.

Phenylalanine is the dietary precursor of tyrosine, dopamine, and norepinephrine. "Precursor loading" treatment of attention deficit disorder with hyperactivity (4) with 1 week of treatment with L-tryptophan yielded minimal behavioral improvement. Moderate but transient improvement in adults with attention deficit disorder, residual type, who were given DL-phenylalanine (587 mg/day) has also been reported (5).

Phenylalanine is of interest for treating hyperactive children; precursor loading may alter the metabolism of neurotransmitters. If there were a deficiency of precursors, of neurotransmitters, or of a metabolic byproduct such as a trace amine in attention deficit disorder with hyperactivity, a precursor loading strategy might be effective. Earlier work suggested that children who have attention deficit disorder with hyperactivity may excrete less phenylethylamine, a trace amine that is a metabolic product of phenylalanine (6). Termination of low-phenylalanine diets in children with phenylketonuria may produce overactivity and inattention (7). A positive correlation between performance on the Continuous Performance Test, a measure of attention, and phenylalanine levels has been reported for children heterozygous for phenylketonuria (8). Finally, aspartame, a new food additive ubiquitous in food consumed by school-age children, contains phenylalanine; in large amounts it can increase serum phenylalanine in normal adults (9). In the present study, we attempted treatment of hyperactive children with D-phenylalanine.

We chose the D isomer because of its enhanced activity (10) in altering central phenylethylamine, the naturally occurring trace amine that has been hypothesized to mediate the clinical effects of amphetamine and methylphenidate (11). D-Phenylalanine is converted to the L type in the periphery also.

METHOD

Eleven male children, ages 6–12 years, were evaluated for impulsive and maladaptive social behavior, hyperactivity, and learning problems. All met the *DSM-III* criteria for attention deficit disorder with hyperactivity; none met the criteria for conduct disorder. Five children had specific developmental disabilities (one spelling and four reading disabilities). Details of the assessment and inclusion and exclusion criteria are described elsewhere (12). Ratings of the children were obtained from community teachers on the 39-item Conners Teacher Rating Scale (13). All of the children were drug free for a minimum of 4 weeks before the study. The protocol was approved by the institutional review board, and consent was obtained from parents and assent from children.

The group had the following characteristics (mean± SD): age, 103±17 months; weight, 29.6±4.6 kg; WISC-R IQ (full scale), 96.7±14. After an outpatient assessment, the children were admitted to the National Institutes of Health Clinical Center for a 48-hour inpatient baseline assessment that included 24-hour urine collection and blood samplings. Cognitive testing included the Continuous Performance Test (14) and

Received May 22, 1986; revised Sept. 5, 1986; accepted Sept. 19, 1986. From the Child Psychiatry Branch, NIMH; and the Adult Psychiatry Branch, NIMH, St. Elizabeths Hospital, Washington, D.C. Address reprint requests to Dr. Zametkin, Child Psychiatry Branch, NIMH, Bldg. 10, Rm. 6N-240, Bethesda, MD 20892.

The authors thank Susan Hamburger, M.S., Eleanor M. Finver, B.A., and Karen Neil for their help.

TABLE 1. Behavioral and Biochemical Effects of D-Phenylalanine and Placebo on 11 Hyperactive Boys

Measure	Baseline		After Placebo		After D-Phenylalanine				
	Mean	SD	Mean	SD	Mean	SD	F[a]	df	p
Continuous Performance Test									
Errors of commission	69.1	96.0	53.0	96.8	50.1	99.1	0.60	1,9	.46
Errors of omission	14.0	8.0	15.0	8.5	13.7	8.6	4.49	1,9	.06
Interstimulus interval (msec)	451.5	52.0	629.1	502.1	475.4	208.4	1.46	1,9	.28
Clinical Global Impression									
Severity index	4.4	1.2	4.0	1.4	4.8	1.0	2.85	1,9	.13
Improvement index			4.0	0.9	4.4	1.3	0.65	1,9	.44
Efficacy index	1.45	4.8	12.27	1.9	11.82	2.1	0.26	1,9	.62
Conners rating scales									
Parents' score	20.4	6.4	15.5	4.9	14.9	7.3	0.68	1,9	.43
Teachers' score	18.5	6.1	17.2	7.3	14.8	6.6	0.46	1,9	.52
Side effects[b]									
Parents' score	26.0	11.1	22.0	9.4	18.7	8.2	3.89	1,8	.08
Doctors' score	13.4	12.4	11.2	8.4	13.1	8.9	0.72	1,9	.42
Serum norepinephrine (pmol/ml)[c]	1.35	0.32	1.46	1.05	1.27	0.39	2.77	1,7	.14
Serum phenylalanine (μmol/liter)	81.9	23.2	86.8	17.8	120.3	20.6	16.60	1,9	.0006
Urinary phenylethylamine (μg/24 hours)	3.05	1.7	2.99	1.0	3.30	1.3	1.77	1,9	.22

[a]Placebo versus D-phenylalanine.
[b]Score on the Treatment Emergent Symptom Scale. The higher the score, the greater the side effects.
[c]N=9.

the Buschke Vigilance Test for recall and consistency of recall (15). While the children were on the inpatient unit, a low-monoamine diet constant for phenylalanine content was maintained. Blood samples were drawn 2 hours after a standard meal and after the noon dose of phenylalanine or placebo.

Following baseline examination, all children were treated with D-phenylalanine and placebo for 2 weeks each in a double-blind crossover study. We increased the dose over the first 3 days of each phase from 10 mg/kg per day to a maximum dose of 20 mg/kg per day, given in four divided doses. The total amount received ranged from 400 mg/day to 700 mg/day (mean±SD=609±94.3 mg/day). Compliance was assessed by counting the number of unused pills returned by the subjects. Weekly parent and teacher ratings on the Conners Parent and Teacher Questionnaire (16) were obtained for the baseline period and for each week of the 4-week study. At the end of each phase, the children were admitted to the inpatient unit for repeat 24-hour urine collection, blood study, Continuous Performance Test, and memory testing. Clinical Global Impression (17, pp. 383–395) scores were obtained at the end of each phase. Side effects were monitored by parents and physicians using the Treatment Emergent Symptom Scale (17, pp. 341–343). Plasma and urine samples were frozen at −80°C until blind analysis could be performed on a single batch. Serum amino acids were quantified by means of a standard Beckman 6300 ion-exchange amino acid analyzer for physiological fluids. Plasma norepinephrine was analyzed by high-pressure liquid chromatography with electrochemical detection. Urinary phenylethylamine and other metabolites were quantified by gas chromatography/mass fragmentography (18).

For all data analysis we used a repeated measures two-way analysis of variance comparing treatment phases (placebo versus drug).

RESULTS

The results of the study are summarized in table 1. There was no significant effect of order of presentation of the drug and placebo. We found no statistically significant behavioral changes on any behavioral measures. There was a trend for fewer errors on omission on the Continuous Performance Test during the phenylalanine phase of the study (p=.06), but errors of commission and the interstimulus interval were essentially unchanged by active treatment. We found no significant change in memory as assessed by the Buschke memory test.

No side effects could be attributed to active treatment. Of the 25 plasma amino acids measured, only phenylalanine was significantly elevated (p=.0006). Serum norepinephrine was unchanged, as were urinary measures of phenylethylamine excretion.

Counts of capsules returned at the end of each phase revealed that 20%±10% of dispensed medication was returned unused.

DISCUSSION

Our major finding was that D-phenylalanine given for 2 weeks in doses that significantly raised serum levels had no therapeutic efficacy for children with attention deficit disorder with hyperactivity. Despite a theoretical basis for the precursor loading strategy, as reviewed by Wurtman et al. (19), this approach was unsuccessful.

The lack of behavioral toxicity, as measured by parent, teacher, and clinician ratings as well as other measures of attention and learning, is encouraging, considering the quantities of phenylalanine now being consumed by school-age children. A rough estimate (9) of phenylalanine consumption in the form of aspartame is about 15 mg/kg per day for adults at the 99th percentile of the distribution of consumers. At this dose, Stegink (20) reported mean±SD peak blood concentrations of phenylalanine of 110±20 μmol/liter, a value comparable to the concentrations reported in this study. Whether or not school-age children consume more aspartame per kilogram of weight is not known, but the dose ingested in this study (20 mg/kg per day) is roughly equivalent to the daily dose that 1% of adults might ingest.

Our finding supports the work of Realmuto et al. (8), who found no significant change in Continuous Performance Test scores after an acute challenge of phenylalanine (100 mg/kg) was given to subjects heterozygous for phenylketonuria. Krause et al. (21), however, did report decrements in performance (increased reaction time) on a neuropsychological test by a group of subjects heterozygous for phenylketonuria during the high-phenylalanine diet phase of a well controlled double-blind study, but serum levels were about 20 times higher than those reported in this study. Our data do not rule out more long-term chronic effects of increased phenylalanine levels.

Compliance in this outpatient study was comparable to that in other reports on compliance (22), possibly because of the non-"drug" nature of this study. Data analysis omitting one subject with particularly poor compliance (47% of pills were returned) did not alter the results.

Phenylalanine failed to increase urinary phenylethylamine despite reports that D-phenylalanine loading can increase the excretion of phenylethylamine five- to tenfold (10). The lack of change in phenylethylamine excretion in this study was unexpected, since highly significant increases in serum phenylalanine were achieved. In summary, a 2-week treatment of children who had attention deficit disorder with hyperactivity produced neither improvement nor deterioration in behavior, providing reassurance about the toxicity of dietary aspartame but arguing against precursor loading treatment of hyperactivity.

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Clinical Characteristics and Response to Sodium Lactate of Patients With Infrequent Panic Attacks

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Nine patients with panic attacks too infrequent to meet DSM-III *criteria for panic disorder were compared to 20 panic disorder patients with respect to clinical characteristics and response to sodium lactate infusion. The two groups showed similar clinical characteristics and response to lactate. The authors conclude that patients with infrequent panic attacks are clinically and biologically similar to those with panic disorder and discuss implications for the diagnosis of panic states.*

(Am J Psychiatry 1987; 144:795–798)

More than 100 years ago, Freud (1) recognized panic attacks as a distinct form of anxiety. In *DSM-III* they were made the basis for the diagnosis of panic disorder, a separate anxiety disorder characterized by the occurrence of at least three panic attacks in a 3-week period. Now several lines of evidence suggest a biological basis for panic disorder: there is a greater prevalence of the disorder in first-degree relatives of affected probands (2), panic disorder can be treated with antidepressants (3) and benzodiazepines (4), and panic symptoms can be provoked in panic disorder patients but not in normal control subjects by intravenous infusion of sodium lactate (5, 6).

Epidemiologic studies have shown that, in addition to the 1%–2% of the population with panic disorder (7), up to 35% of the population reports panic attacks too infrequent to meet criteria for panic disorder (8, 9). Patients with infrequent panic attacks resemble those with panic disorder in demographic characteristics (8), depression and anxiety scores, and prevalence of a history of major depression (9, 10). The prevalence of mitral valve prolapse in these patients is similar to that of panic disorder patients and is significantly higher than that of patients with generalized anxiety disorder without panic attacks (11). We studied clinical variables and response to sodium lactate of a group of patients with infrequent panic attacks to clarify further their biological and clinical relationship to patients with panic disorder.

METHOD

Patients were seen at an anxiety disorders clinic; they met *DSM-III* criteria for panic disorder without agoraphobia or limited phobic avoidance (N=20) or had panic attacks as described in *DSM-III* but at a frequency of once a year to twice a month (N=9). The average number of panic attacks per year in the latter group was 7.1, and only one patient had attacks more often than once a month. Eight of these nine subjects also met *DSM-III* criteria for generalized anxiety disorder. Only one of the nine had a past history of panic disorder. The Hamilton Rating Scale for Anxiety, the Hamilton Rating Scale for Depression, and the SCL-90 (12) were completed for each patient.

These 29 patients and 10 control subjects who had no personal or family history of panic attacks or affective illness underwent lactate infusions. The subjects included 19 men and 20 women between 18 and 65 years of age. There were no significant age or sex differences among the three diagnostic groups.

All subjects were medication free for at least 2 weeks before the lactate infusion and underwent a full medical evaluation. Exclusion criteria were alcohol or substance abuse within the past 6 months or major hepatic, renal, endocrine, pulmonary, or cardiovascular disease (except possible mitral valve prolapse). Written informed consent was obtained after the procedure was fully explained.

Lactate infusions were done in the morning, after subjects had fasted and abstained from caffeine and tobacco for at least 3 hours. Normal saline was given as a slow intravenous infusion for 10 minutes, then at a rate comparable to the subsequent lactate infusion for 5 minutes. The infusion was then changed under single-blind conditions to 0.5 M sodium lactate, 10 cc/kg, which was given over 20 minutes. All solutions were warmed to body temperature. Vital signs and an

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The authors thank Kathy Ahern-Murphy, Chris Budech, Kathy Daman, Nancy Renn, Mary Ann Curulla, and Corinne Maddock for technical assistance and Marcy Hall for manuscript preparation.

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ECG were monitored throughout the procedure. The infusion was stopped if a panic attack occurred.

At 5-minute intervals, the physician in attendance completed the Acute Panic Inventory, a 16-item scale used to record a patient's subjective experience of symptoms classically experienced during panic attacks, such as fear of dying, feeling of impending doom, palpitations, and difficulty breathing (6). Infusions were done and responses judged by physicians blind to the subjects' diagnoses and to the frequency of their panic attacks.

A positive response to lactate was defined as the subject's experiencing enough physical symptoms to meet *DSM-III* criteria for a panic attack and an increase in anxiety of at least 2 points on the 10-point scale to at least 4 out of 10. This also had to be experienced by the patient as a considerable increase in anxiety. A panic response was defined as a positive response accompanied by the sudden onset of terror or panic.

The proportions of patients in each diagnostic group who experienced a positive or panic response to lactate were compared by chi-square tests. Clinical characteristics of the patients with infrequent panic attacks and the patients with panic disorder were compared by t tests. A one-way analysis of variance was used to determine differences among the three diagnostic groups in baseline, peak, and net peak (peak minus start of lactate) panic inventory and anxiety scores.

RESULTS

Clinical characteristics of the panic disorder patients and those with infrequent panic attacks are shown in table 1. There were no significant differences between the two groups in age at first panic attack, duration of illness, Hamilton anxiety and depression scores, SCL-90 total score, or scores for the SCL-90 subscales of anxiety, depression, and somatization. There was a significant difference only in SCL-90 phobic anxiety scores, with panic disorder patients having higher scores. Four of the 20 panic disorder patients and three of the nine patients with infrequent panic attacks reported a past history of major depression. This difference was not statistically significant according to a chi-square test.

Eight of the nine patients with infrequent panic attacks had a positive response to lactate, and four of these eight reported a panic attack. These attacks were similar to their spontaneous attacks. For example, one patient experienced "my body burning" as a prominent part of spontaneous attacks and reported this symptom during lactate infusion. Of the 20 panic disorder patients, 17 had a positive response and nine reported a typical panic attack. There were no statistically significant differences between the two groups in the proportion of patients with positive or typical panic responses to lactate. One normal control subject reported a positive response, but no control subject had a panic attack during lactate infusion. Patients with infrequent panic attacks had a significantly greater rate of positive responses ($\chi^2=11.6$, df=1, $p<.001$) and typical panic responses ($\chi^2=5.6$, df=1, $p<.02$) than did control subjects. Panic disorder patients also differed significantly from control subjects in the rate of positive ($\chi^2=15.6$, df=1, $p<.001$) and typical ($\chi^2=6.4$, df=1, $p<.02$) panic responses.

TABLE 1. Clinical Characteristics of Patients With Panic Disorder (N=20) and Patients With Infrequent Panic Attacks (N=9)

Clinical Variable	Patients With Panic Disorder		Patients With Infrequent Panic Attacks	
	Mean	SD	Mean	SD
Hamilton anxiety score	21.6	6.3	23.9	6.9
Hamilton depression score	11.0	4.6	13.0	3.6
Duration of panic attacks (years)	7.6	10.2	10.2	8.0
Age at onset of panic attacks (years)	29.2	10.1	30.2	3.9
SCL-90				
Total score	76.0	51.6	81.8	41.0
Subscale scores				
Anxiety	13.6	6.9	12.4	5.4
Depression	11.0	10.0	16.3	10.5
Somatization	12.2	6.2	9.1	5.3
Phobic anxiety[a]	5.4	3.1	2.0	2.5

[a]Significant difference between groups (t=2.9, df=13, p=.01).

The mean±SD time of peak symptoms was after 14.6±5.8 minutes of lactate for panic disorder patients, 14.9±5.5 minutes for those with infrequent panic attacks, and 18.8±5.7 minutes for control subjects. Although both groups of patients showed earlier mean peak response times than control subjects, this difference did not reach statistical significance.

Patients with infrequent panic attacks were similar to panic disorder patients in the pattern of their response to lactate. Even when baseline differences were taken into account (13), there were no statistically significant differences between these two groups in panic inventory scores and anxiety scores over the course of the infusion. Both groups differed significantly from the normal control group in changes in panic inventory scores ($F=5.7$, df=2, 35, $p=.007$) and anxiety scores ($F=7.3$, df=2, 35, $p=.002$) with lactate.

DISCUSSION

Our data show that patients with infrequent panic attacks were similar to those with panic disorder both clinically and in their response to sodium lactate infusion. This has important implications for the diagnostic specificity of lactate infusion and for the diagnosis and treatment of panic states. In our sample, patients with infrequent panic attacks were similar to panic disorder patients and significantly different from control subjects in the rate and pattern of their response to lactate. These results add to the increasing evidence that sensitivity to lactate is specific not for

panic disorder but for the phenomenon of panic attacks (14–18). Furthermore, they show that response to lactate is independent of the frequency of attacks. Interestingly, the first study of lactate infusions in patients with infrequent panic attacks may have been the work of Pitts and McClure, whose pioneering study of the effects of sodium lactate (5) involved patients with anxiety neurosis, many of whom probably had panic attacks too infrequent to meet *DSM-III* criteria for panic disorder.

The high rate of response to lactate of the patients with infrequent panic attacks suggests that the response may be a trait rather than a state marker for panic. Studies of response to lactate in patients with a more distant history of panic would help to clarify this point. Additional studies of lactate infusions in patients with generalized anxiety disorder with and without infrequent panic attacks are also necessary to replicate our findings and to further investigate the specificity of response to lactate within anxiety disorders.

Both the patients with panic disorder and those with infrequent panic attacks had a 85%–90% rate of positive response to lactate as we have defined it. This is considerably higher than the rate of typical panic attack responses found in this study and by other groups (6). Only one of 10 control subjects had a positive response to lactate. Thus, a positive response, as we have defined it, may prove to be a more sensitive but still specific way of differentiating panic patients from control subjects when lactate infusion or other biological challenges are used. It is interesting that our definition of a positive response yields lactate response rates in patients and control subjects similar to those reported by Pitts and McClure (5).

Our data give clinical and biological evidence to support the elimination of the requirement of three panic attacks in a 3-week period to make the diagnosis of panic disorder. As reported by other groups (9, 10), the patients with infrequent panic attacks resembled the panic disorder patients clinically. The only significant difference was in SCL-90 phobic anxiety scores, which were higher in the panic disorder patients, even though they did not have agoraphobia or limited phobic avoidance. More frequent panic attacks may cause more phobic avoidance. Alternatively, differences in coping strategies (10), especially if these predate the onset of panic attacks, could influence both the frequency of attacks and the degree of phobic anxiety that results.

There was no significant difference between the two groups of patients in duration of illness or age at onset, although patients with infrequent attacks tended to have had panic attacks over a longer period of time. This suggests that patients with infrequent panic attacks do not necessarily move on to panic disorder and that the similarities we observed were not due to our studying the patients at an earlier stage of the same disorder.

We present new evidence for a biological link between panic disorder and infrequent panic attacks. The two groups of patients had comparable rates of positive and typical panic responses to lactate as well as the similar prevalence of mitral valve prolapse that was previously reported by our group (11). Thus, panic attacks most likely represent a distinct biological entity that occurs with variable severity and frequency. Frequency of attacks does not seem to demarcate a clinically or biologically separate phenomenon. Instead, it may indicate the severity of an underlying biological defect or differences in psychological factors and coping strategies.

In our clinical experience, the current criteria for panic disorder often lead to classification of patients with infrequent panic attacks as having generalized anxiety disorder, since infrequent panic attacks are not an exclusion criterion for this diagnosis. This confuses the diagnosis of generalized anxiety disorder as well as that of panic disorder. An alternative approach to diagnosis might be to consider panic a single phenomenon that occurs on a continuum of frequency and severity, with further subdivision of panic states on the basis of differences in etiology, once these are clarified.

Frequency of panic attacks is important in judging the benefit versus the cost of daily medication. However, our results suggest that patients with less frequent panic attacks may benefit from the same treatments that are used for panic disorder, especially in the presence of serious distress or dysfunction.

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Electrocardiographic Effects of Nortriptyline, Phenelzine, and Placebo Under Optimal Treatment Conditions

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The authors treated 44 outpatients 55 years old or older who were suffering from major depression with either nortriptyline, phenelzine, or placebo for 7 weeks. Plasma levels of nortriptyline were kept between 50 and 170 ng/ml, and platelet monoamine oxidase (MAO) inhibition in phenelzine-treated patients was kept between 70% and 80%. ECGs were compared before and after treatment. Nortriptyline produced statistically significant increases in both the heart rate and the PR interval, although none was outside the normal range. Phenelzine produced a significant decrease in the QT interval. None of the patients had pathological ECG changes under the closely monitored treatment conditions of this study.

(Am J Psychiatry 1987; 144:798–801)

Although many clinicians are aware of the suffering of elderly people who are depressed, there is often a reluctance to use antidepressants in this population because of the fear of side effects, particularly those affecting the cardiovascular system. As a result, many older patients with major depression, especially those with cardiovascular disease, are not treated with antidepressants or are treated with suboptimal doses of them (1). Elsewhere (2), we stated that under optimal conditions, depression in the elderly can be successfully treated with either nortriptyline or phenelzine with minimal side effects. In addition, both drugs appear to be equally efficacious. We wish now to report on the electrocardiographic changes that occurred in our patients during treatment.

Nortriptyline as a tricyclic antidepressant is believed to exert an effect on the myocardium like that of quinidine (3) and may result in negative inotropy, delayed intraventricular conduction, and a prolonged QT interval. There have been reports of nortriptyline prolonging intraventricular conduction in patients (4, 5), but these findings have been criticized because the plasma levels of nortriptyline used were much higher (greater than 180 ng/ml) than those considered optimal. Other studies have reported no significant electrocardiographic effects of nortriptyline except for increased heart rate (6–8). The increase in heart rate is believed to be due to the anticholinergic effect of nortriptyline on the sinoatrial node.

The electrocardiographic effects of phenelzine have been less frequently studied (9). Robinson et al. (10) reported that phenelzine-treated patients had decreases in heart rate and shortening of the QT interval but that there was no effect on the PR interval or QRS complex. These changes are believed to be mediated through the sympatholytic effect of monoamine oxidase (MAO) inhibitors.

The present report focuses on the electrocardio-

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Supported by NIMH grant MH-35196 to Dr. Georgotas.

The authors thank Irene Chang for her contribution as project director, Ethel Edelstein for secretarial assistance, David Allen and Brenda Katos for nortriptyline assays, and Joan Kuster for monoamine oxidase assays.

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graphic changes observed under placebo-controlled conditions in elderly patients who were treated with either nortriptyline or phenelzine.

METHOD

The patients in this report were part of a larger treatment study of 75 depressed outpatients, 55 years old or older (range=55–82 years; mean±SD=64.9± 6.3 years), who attended the Depression Studies Program of New York University (2). Patients included in the study were diagnosed independently by two concurring psychiatrists (A.G. and R.E.M.) as suffering from a major depressive disorder as defined by Research Diagnostic Criteria (RDC) (11). In addition, a score of 16 or greater on the 21-item Hamilton Rating Scale for Depression was required. Patients were excluded if they showed evidence of moderate to severe dementia or other preexisting psychiatric disorders (e.g., schizophrenia, drug dependence, or alcohol dependence).

Before treatment, patients were given a physical examination and a battery of clinical laboratory evaluations. Patients with preexisting cardiac problems were required to obtain clearance from their cardiologist before entering the protocol. Patients were not excluded from the protocol for any cardiac disease or conduction abnormalities, provided that they had obtained clearance from and we could treat them in close cooperation with their cardiologist. Of 137 patients accepted for the study, 18 (13%) did not enter the protocol because they could not get cardiac clearance. However, none of the patients who entered the protocol was excluded from the data analysis or prematurely terminated from the study because of cardiac problems.

At the end of a 1-week single-blind placebo period, patients with a Hamilton depression rating of 16 or more entered the 7-week double-blind treatment phase in which they were sequentially assigned to one of three treatment conditions—nortriptyline, phenelzine, or placebo—by means of a previously randomized medication code. All three substances were prepared in identically appearing capsules containing 25 mg of nortriptyline, 15 mg of phenelzine, or an inert substance. Dosage was adjusted according to clinical condition, but all patients receiving nortriptyline were maintained at a plasma level between 50 and 170 ng/ml and all phenelzine patients had achieved platelet MAO inhibition above 70%. Drug accountability, dosage, and concomitant medication records were carefully maintained throughout the study.

During each of the seven weekly visits, drug efficacy and safety were evaluated by a physician blind to the study condition (R.E.M.). ECGs were performed before treatment, at the end of the third week of treatment, and at the final week of treatment. Measurements of the PR interval, QRS duration, QT interval, and heart rate were made at the time of screening and after 7 weeks of treatment by a physician blind to the patient's treatment status (R.E.M.). Measurements were made on lead II. Matched-pair t tests were used to compare differences in the PR interval, QRS duration, QT_c (QT interval corrected for heart rate) (12), and heart rate. Data from the 44 patients who completed 7 weeks of treatment and who had the complete series of ECGs are presented here.

In the placebo group, two patients had known cardiac disease: one had had a myocardial infarction with subsequent infrequent episodes of angina, and the other had had a triple coronary artery bypass and was asymptomatic. Another patient with no known cardiac disease had first-degree atrioventricular block on the baseline ECG. One patient in the placebo group was taking propranolol for hypertension.

In the nortriptyline group, three patients had known cardiac disease: one patient had had a myocardial infarction and was asymptomatic, and the other two had had rheumatic fever with subsequent valvular heart disease and minimal symptoms. In addition, one patient with no known heart disease was found to have first-degree atrioventricular block on the baseline ECG. None of the nortriptyline patients was taking cardiac medications except for one of the patients with rheumatic heart disease, who took a small dose of propranolol (10 mg) for palpitations.

In the phenelzine group, only one patient had known cardiac disease—mitral valve prolapse—from which she had minimal symptoms. One patient with no known cardiac disease was found to have an intraventricular conduction delay at baseline. None of the phenelzine patients was taking concomitant cardiac medications.

None of the patients studied had unstable angina or congestive heart failure. All patients had sinus rhythm on their ECGs at baseline.

RESULTS

Of the 44 patients, 14 were treated with placebo, 16 were treated with nortriptyline, and 14 were treated with phenelzine. At the end of 7 weeks of treatment, one (7%) of the placebo patients, 12 (75%) of the nortriptyline patients, and eight (57%) of the phenelzine patients were responders (Hamilton score less than 10).

The mean±SD plasma level of nortriptyline after the second week of treatment was 90.4±5.4 ng/ml (range=82.6–96.0 ng/ml). In the phenelzine group, the mean±SD percentage of platelet MAO inhibition after the second week of treatment was 78.5%±2.7% (range=74.1%–81.1%).

The changes in ECG measures with treatment are illustrated in table 1. Statistically significant changes in the PR interval, a measure of atrial depolarization and atrioventricular node conduction, were noted in both the placebo and nortriptyline treatment groups. There was a significant decrease in the PR interval of place-

TABLE 1. Electrocardiographic Measures in 44 Patients Before and After Treatment With Placebo, Nortriptyline, or Phenelzine

Treatment Group	PR Interval (seconds)		QRS Duration (seconds)		QT Interval (seconds)		QT_c Interval (seconds)		Heart Rate	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Patients given placebo (N=14)										
Before treatment	0.18	0.01	0.06	0.01	0.37	0.03	0.39	0.04	69.5	17.5
After treatment	0.17	0.02	0.07	0.02			0.40	0.03	75.7	17.6
Change	−0.01[a]	0.01	0.01	0.01			0.01	0.04	6.2	12.8
Patients given nortriptyline (N=16)										
Before treatment	0.16	0.02	0.07	0.02	0.40	0.04	0.43	0.06	70.2	11.7
After treatment	0.18	0.02	0.07	0.02			0.45	0.07	84.0	13.9
Change	0.02[b]	0.02	0.00	0.02			0.02	0.03	13.8[c]	9.5
Patients given phenelzine (N=14)										
Before treatment	0.16	0.02	0.06	0.02	0.37	0.04	0.43	0.03	79.1	16.2
After treatment	0.17	0.02	0.06	0.02			0.41	0.03	77.2	14.0
Change	0.00	0.01	0.00	0.01			−0.02[d]	0.02	−1.9	13.1

[a]Significantly different ($t=-2.52$, $df=13$, $p<.05$).
[b]Significantly different ($t=3.06$, $df=15$, $p<.01$).
[c]Significantly different ($t=5.79$, $df=15$, $p<.01$).
[d]Significantly different ($t=-3.95$, $df=13$, $p<.01$).

bo-treated patients after 7 weeks of treatment. On the other hand, nortriptyline patients had a significant increase in the PR interval. No significant changes in the PR interval were noted in the phenelzine group. None of the changes caused the PR interval to fall outside of the normal range (0.12–0.20 seconds). One patient in the placebo group and one patient in the nortriptyline group had first-degree atrioventricular block (PR interval=0.24 seconds) at baseline; this was not exacerbated in either patient by 7 weeks of treatment.

There were no significant changes in the QRS duration, a measure of ventricular depolarization, in any of the three groups. One patient in the phenelzine group had an intraventricular conduction delay (QRS duration=0.12 seconds) at baseline, but there was no change in this after treatment.

The QT interval, a measure of both ventricular depolarization and repolarization, has a range of normal values that is dependent on both sex and heart rate. Five patients (three receiving nortriptyline and two receiving phenelzine) had a mild-to-moderately prolonged QT at screening. In three of these patients, this persisted throughout treatment. In the other two patients (one receiving nortriptyline and one receiving phenelzine), the QT interval was within normal limits after 7 weeks of treatment. One patient in the nortriptyline group had a prolonged QT interval at week 7, although he did not have one at screening. Using the QT_c to compare changes with treatment, we found no significant changes in the QT_c interval in the placebo and the nortriptyline groups; however, patients treated with phenelzine had a significant decrease in the QT_c interval after treatment (table 1).

The heart rate of nortriptyline-treated patients increased significantly during treatment (table 1). No significant changes were found in the rates of patients in the placebo and phenelzine groups.

In summary, nortriptyline appeared to produce significant changes in cardiac physiology as measured by the ECG. Significant increases in the heart rate and the PR interval were found after 7 weeks of treatment with nortriptyline, although none was large enough to be outside the normal range. Phenelzine-treated patients had a significant decrease in QT_c interval, and there was a significant decrease in the PR interval in placebo-treated patients, but these were not outside the normal range. No significant pattern emerged from changes in the QRS duration.

DISCUSSION

In our group of elderly patients treated with nortriptyline for major depression, there was a statistically significant increase in PR interval and heart rate. These results are not surprising because other studies have found that nortriptyline increases heart rate (6–8). Given that tricyclic antidepressants like nortriptyline are believed to suppress myocardial electrical activity as quinidine does, it is equally unsurprising that there was a statistically significant increase in the PR interval in the nortriptyline group. What should be emphasized, however, is that in no case did the heart rate or PR interval increase beyond normal limits.

The sole patient in the nortriptyline group with first-degree atrioventricular block had no change in PR interval after treatment. There were no significant changes in the QRS duration or QT interval. These less than extreme electrocardiographic changes are heartening because our patient population was elderly and patients with known cardiovascular disease were not excluded from treatment as long as they were stable and had received clearance from their cardiologists. It is quite possible that our controlling for plasma levels of nortriptyline accounts for this; several studies (13) have shown that the incidence of side effects of most tricyclic antidepressants increases at plasma levels

above the therapeutic range. With nortriptyline in particular, alarming ECG changes have been described, mainly in patients with high plasma levels (usually exceeding 200 ng/ml) (14, 15). None of our patients' levels exceeded 170 ng/ml.

Phenelzine produced a significant decrease in the QT_c interval; this finding supports those of Robinson et al. (10). No significant changes were found in PR interval, QRS duration, or heart rate. This is probably due to the fact that only modest doses of phenelzine were used; the mean platelet MAO inhibition ranged from 70% to 80% throughout the treatment period, and most of our patients responded at this range. The reduction of the PR interval in the placebo-treated patients cannot easily be accounted for but should remind us of the inherent variability of all biological data, including electrocardiographic data.

Our findings suggest that although antidepressants such as nortriptyline and phenelzine may have measurable effects on cardiac physiology, their use is not precluded in elderly patients on an outpatient basis when treatment is closely monitored and plasma levels are kept within the optimal range. None of our patients, even those with posttreatment ECG changes, had clinical signs of cardiac decompensation during treatment. However, caution is still advisable because additional studies of antidepressant effects in the elderly are needed. In addition, a more technologically sophisticated investigation of cardiophysiological changes with antidepressant treatment may provide a clearer understanding of the effect of these drugs on the heart in older patients.

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Comparison of Propranolol, Sotalol, and Betaxolol in the Treatment of Neuroleptic-Induced Akathisia

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In earlier open studies, β-blockers were found to be effective in the treatment of neuroleptic-induced akathisia. In the present study, 16 patients with severe neuroleptic-induced akathisia successively received low doses of three β-blockers—propranolol, sotalol, and betaxolol. There was rapid and complete improvement in seven of 16 patients (and partial improvement in three patients) treated with propranolol and in all four patients treated with betaxolol. The efficacy of propranolol and betaxolol and failure of sotalol in treating neuroleptic-induced akathisia suggest a central mechanism of action.
(Am J Psychiatry 1987; 144:802–805)

The term "akathisia" was created by Haskovec in 1901 (1); its literal translation is "inability to remain seated." At the present time this term refers almost exclusively to a side effect of neuroleptic drugs. It is characterized by a subjective sensation of discomfort, agitation, and motor hyperactivity ranging from frequent changes of posture to incessant limb shaking and inability to remain seated for more than a short period of time. While at times patients do not complain of these symptoms, the aimless activity is poorly tolerated by others. The frequency of neuroleptic-induced akathisia ranges from 5% to 45% (2–4); 20% seems to be the most common estimate (5). The treatment of akathisia is difficult. Although anticholinergic drugs (6), amantadine (7), and benzodiazepines (8, 9) are effective in some cases, they are most often of limited benefit. Lipinski et al. (10, 11) proposed a link between akathisia and the restless legs syndrome described by Ekbom (12). Taking into account the work of Strang (13), they evaluated the effects of propranolol in the treatment of neuroleptic-induced akathisia. Comparing these effects to those of metoprolol (14), they proposed a central β_2-adrenergic mechanism of action.

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In order to elucidate, if not the precise mechanism of β-blocking agents in akathisia, at least whether or not the effects of β-antagonists are central or peripheral and whether β_1- and β_2-adrenoceptors mediate the effects, we compared the effects of three β-blocking agents—propranolol (a nonselective β_1- and β_2-blocker that is lipophilic and thus will enter the brain readily), sotalol (a nonselective β_1- and β_2-blocker that is hydrophilic and enters the brain poorly), and betaxolol (a lipophilic β-blocker with higher affinity for β_1- than for β_2-adrenoceptors).

METHOD

This open trial was carried out with 16 patients (table 1) who had neuroleptic-induced akathisia and had no contraindications for the use of β-blocking agents. The akathisia rating scale proposed by Chouinard et al. (15, 16) includes a subjective evaluation, rated 0–3, and an objective evaluation, rated 0–6. Only the latter was used in this trial for the selection of patients and evaluation of drug effects. The ratings were done by two independent raters at 8:00 a.m., i.e., during the β-blocker sequences 12 hours after drug administration.

Regardless of each patient's akathisia score at the time of inclusion or during drug washout periods, only the disappearance of akathisia (decrease to score of 0) within 48 hours of β-blocker treatment was considered a positive response.

The 16 patients selected for study received 20 mg of propranolol as a single daily oral dose for 2 days. For patients who had a positive response, treatment was maintained for 6 months. For patients who did not respond, the dose was doubled on the third day. If that dose did not suppress akathisia within 2 days, the patient was excluded from the study. At the end of 6 months, there was a drug washout period of 2 weeks to ascertain that akathisia recurred. At the end of this washout period the patients received sotalol (40 mg/day) for 2 days; if there was no response, the daily dose was doubled. After a second 2-week washout period, patients received betaxolol (10 mg/day) for 2 days; if there was no response, the daily dose was doubled for at least 2 days.

TABLE 1. Data on 16 Subjects Given Propranolol for Treatment of Neuroleptic-Induced Akathisia

Patient	Age (years)	Sex	Diagnosis	Other Drugs	Propranolol Dose (mg/day)	Akathisia Score	
						Before Propranolol	2 Days After Propranolol
1	46	F	Chronic paranoid schizophrenia	Levomepromazine, pipotiazine/ trihexyphenidyl	40	4	4
2	62	M	Chronic undifferentiated schizophrenia	Levomepromazine, loxapine, alimemazine/phenobarbital	40	5	2
3	47	M	Chronic paranoid schizophrenia	Haloperidol, droperidol, cyamemazine/trihexyphenidyl	20	4	0
4	57	M	Chronic paranoid schizophrenia	Haloperidol, chlorpromazine/ trihexyphenidyl	20	4	0
5	23	M	Antisocial personality disorder	Haloperidol, cyamemazine/ trihexyphenidyl	40	4	0
6	72	F	Bipolar disorder, manic	Haloperidol, levomepromazine/ trihexyphenidyl, phenobarbital	40	4	1
7	38	M	Chronic undifferentiated schizophrenia	Levomepromazine, sultopride	40	6	4
8	43	M	Chronic disorganized schizophrenia	Pipotiazine	20	5	0
9	49	F	Moderate mental retardation, intermittent explosive disorder	Levomepromazine, pipotiazine	20	4	0
10	22	F	Chronic undifferentiated schizophrenia	Levomepromazine, chlorpromazine/ trihexyphenidyl	40	4	4
11	28	M	Chronic catatonic schizophrenia	Flupentixol/trihexyphenidyl	40	4	4
12	22	F	Borderline personality disorder	Flupentixol, sulpiride/ trihexyphenidyl	20	2	0
13	44	M	Chronic undifferentiated schizophrenia	Chlorpromazine, pipotiazine/ trihexyphenidyl	40	4	4
14	57	M	Chronic paranoid schizophrenia	Haloperidol/trihexyphenidyl	20	4	0
15	21	F	Atypical psychosis	Pipotiazine/trihexyphenidyl	20	4	0
16	71	F	Paranoid disorder	Haloperidol, perphenazine	40	4	4

The doses of propranolol (20 and 40 mg), sotalol (40 and 80 mg), and betaxolol (10 and 20 mg) are considered equivalent (17).

RESULTS

Propranolol treatment was successful in eight patients, seven of whom received 20 mg/day and one 40 mg/day (table 1). Three of the remaining eight patients demonstrated partial improvement. Effects were always observed within 48 hours of treatment. No relationship between response to propranolol and the patient's or neuroleptic's characteristics could be established. Seven patients (subjects 3, 5, 8, 9, 12, 14, and 15) maintained a score of 0 during the following 6 months and entered into the trial. Akathisia recurred after 9 weeks in patient 4, who was therefore excluded from the study.

Since one patient (subject 5) was transferred to another hospital, only six patients entered the 2-week washout period. In all patients, akathisia returned to the initial level during this period. In all six patients sotalol, 40 mg/day for 2 days followed by 80 mg/day for 2 days, failed to suppress the symptoms of akathisia.

Two patients could not complete the trial; in one case (subject 14), the patient left the hospital because of psychiatric improvement, and in the other (subject 15), a decrease in neuroleptic dose resulted in the disappearance of akathisia. The four remaining patients experienced the recurrence of akathisia during the third washout period; the akathisia disappeared within 2 days of treatment with betaxolol, 10 or 20 mg/day.

DISCUSSION

This study confirms the previously reported efficacy of propranolol in treating neuroleptic-induced akathisia (11, 14, 18). The stringency of our criteria for a positive response (decrease to score of 0, low dose, rapid onset of action, and efficacy maintained during 6 months) could explain the smaller success rate in our study (seven of 16 patients) than in Lipinski et al.'s trial (11) (nine of 14 patients). Since both were open studies and since a dose-response relationship has not been established, such a difference is unlikely to be significant.

The lack of a rapid effect of sotalol (the only β-blocking agent with a negative octanol/water partition coefficient [−0.79] and therefore the most hydrophilic agent) leads us to propose, as did Lipinski et al. (11), a central mechanism of action, since only lipophilicity permits a rapid rate of penetration of the drug into the CNS.

However, Ratey et al. (19) reported three cases of patients with neuroleptic-induced akathisia who were successfully treated by the poorly lipophilic β-blocking

agent nadolol. Moreover, those authors proposed a peripheral mechanism. Three points have to be considered.

1. Nadolol is not a pure hydrophilic compound.
2. It is more lipophilic than sotalol (octanol/water partition of +0.71 versus −0.79 for sotalol).
3. Animal studies (20, 21) have shown that while levels of highly lipid-soluble propranolol and alprenolol equilibrate rapidly between brain and plasma, hydrophilic β-blocking agents, such as practolol, have also been found in the brains of dogs after oral administration. However, the rate of transfer to the brain and the equilibrium ratio of brain/plasma drug concentration were lower than for the more lipid-soluble drugs (22). Similar CNS penetration of the hydrophilic atenolol has been measured in man (23, 24), leading to central actions (25).

Therefore a central effect cannot be dismissed if the full effect is not observed within a short period of time. Ratey et al. (19) found that the total disappearance of akathisia occurred after 1 week of treatment for the first patient and 2 weeks for the third; the time course was not specified for the second patient, and improvement was only partial, necessitating the addition of lorazepam.

Betaxolol is a lipophilic and highly selective β_1-blocking agent (26). Its selectivity ratio (ratio between the concentration necessary to block β_1-receptors and the concentration necessary to block β_2-receptors) is 245, compared to 155 for metoprolol and 4 for propranolol (27). At low doses, β_2-blockade is unlikely to occur and is not clinically significant. In the present study, betaxolol acted rapidly and completely in all patients, which suggests a central β_1 mechanism of action.

Zubenko et al. (14) compared metoprolol (a highly lipophilic drug that at low doses is a relatively selective antagonist of the β_2-receptor and at higher doses, i.e., more than 100 mg/day, is a nonselective antagonist of both β_1- and β_2-receptors) to propranolol in the treatment of neuroleptic-induced akathisia. The mean dose necessary for improvement was 300 mg/day of metoprolol. On the basis of these findings in five patients, those investigators suggested that β_2-receptor antagonism was responsible for the improvement, for if β_1-receptor antagonism alone were sufficient, metoprolol at doses of less than 100 mg/day should have been effective. The present study of betaxolol, which is more selective than metoprolol for the β_1-receptor, failed to confirm the earlier findings and suggests that central β_1-blockade is sufficient. Since both the previous and present studies were open and involved small numbers of patients (five and four, respectively), further research is necessary to determine whether β_1-, β_2-, or β_1- plus β_2-receptor blockade is responsible for the clinical effects.

The efficacy of propranolol and betaxolol and the failure of sotalol in treating neuroleptic-induced akathisia lead us to suggest that in this syndrome, β-blocking agents act mainly, if not exclusively, through a central β_1 mechanism. Double-blind controlled studies are needed to confirm this hypothesis.

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Spontaneous Remission of MAOI-Induced Anorgasmia

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The authors present three case reports illustrating that a conservative approach to anorgasmia induced by effective treatment with the monoamine oxidase inhibitor (MAOI) phenelzine can result in spontaneous remission. Precipitously stopping phenelzine or adding another medication to counteract the side effect can be avoided. The apparent synchrony between the development of the side effect of anorgasmia and positive treatment response may represent a valuable clinical marker.
(Am J Psychiatry 1987; 144:805–807)

There has been a marked renewal of interest in the clinical use of monoamine oxidase inhibitors (MAOIs) for various psychiatric disorders. Their ability to produce sexual dysfunction is more prevalent than the well-publicized adverse effects of hypotension, liver toxicity, or hypertensive crisis. This takes on added importance in view of the fact that patients taking these drugs expect normal sexual function as part of their treatment outcome. In this report we present a new finding of spontaneous reversal of MAOI-induced anorgasmia with continued treatment at therapeutic levels of phenelzine. The finding expands the present clinical knowledge base and has both practical and theoretical implications.

CASE REPORTS

Case 1. Ms. A, a 27-year-old graduate student, was suffering from panic disorder and depression. The former responded to an 8-week course of imipramine, 300 mg/day, but the latter did not. After her treatment was changed to phenelzine, 60 mg/day, both the panic and the depression responded. At week 4 of phenelzine treatment, the patient reported the absence of orgasm during sexual intercourse. There had been no change in her sexual practices.

With clinical improvement, she described a renewed interest in sex, which had declined while she was ill. Arousal, excitation, and lubrication were intact. Orgasm had been present both before and during the time she was depressed. Reduction of phenelzine to 45 mg/day resulted in the return of both orgasm and panic attacks. The patient insisted on increasing her dose of phenelzine, stating that sexual dysfunction was preferable to experiencing panic attacks. Other than mild orthostasis, no other side effects were noted.

Phenelzine, 60 mg/day, was reinstituted as the minimal necessary dose for symptom control despite anorgasmia. At week 16 Ms. A reported a spontaneous return of her ability to experience orgasm. This continued to 1 year of follow-up. Two attempts gradually to discontinue phenelzine at 6 months and at 12 months resulted in return of panic.

Case 2. Mr. B, a 24-year-old accountant, experienced a relapse of major depression marked by sleep and appetite disturbance, psychomotor retardation, and melancholia. He had been successfully treated 3 years earlier with nortriptyline, 100 mg/day. During remission, he had maintained regular satisfying sexual relations with his spouse. He had no previous history of sexual dysfunction, substance abuse, or medical illness.

Treatment with nortriptyline, 100 mg/day (serum level, 115 ng/ml), for 6 weeks produced minimal improvement. Conversion to phenelzine was instituted, and the dose was gradually increased over a 2-week period to 75 mg/day as the dose of nortriptyline was gradually discontinued. Mr. B's depression remitted after 3 weeks of phenelzine administration alone. He reported a substantial improvement in libido but became unable to ejaculate. The sexual act no longer felt pleasurable despite strong desire and erectile potency. There were no other substantial side effects from the medication.

Mr. B's ejaculatory dysfunction persisted for another 3 weeks and then improved spontaneously. He experienced no recurrence of sexual difficulties while taking 75 mg/day of phenelzine during a 4-month follow-up.

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Case 3. Ms. C, a 29-year-old woman, was suffering from rejection-sensitive dysphoria and atypical depression. Treatment with phenelzine, 75 mg/day, produced a marked improvement in her sense of well-being, sensitivity to criticism, hypersomnia, and craving for sweets. After 3 weeks of treatment, however, she reported that she could no longer achieve orgasm by masturbation or intercourse. Excitement, arousal, and lubrication were intact. She had no previous history of anorgasmia. Lowering the dose of phenelzine to 45 mg/day failed to correct the sexual dysfunction but maintained clinical improvement. She insisted on continuing pharmacotherapy despite sexual dysfunction.

An attempt to substitute tranylcypromine, 20 mg/day, at week 12 was unsuccessful due to orthostasis, a dysphoric "racy feeling," and continued sexual dysfunction. Phenelzine, 45 mg/day, was reinstated. At week 20, Ms. C reported that she was again orgasmic during both masturbation and intercourse. After 1-year follow-up, she continued to take maintenance phenelzine, 45 mg/day, without side effects.

DISCUSSION

The three patients described here developed sexual dysfunction in association with MAOI treatment at therapeutic doses. There was a delayed drug effect that seemed to parallel improvement in symptoms. Dose reduction to levels that maintained clinical improvement did not reverse the side effect. Sexual arousal, responsivity, and libido were unaffected. Because of fear of relapse, the patients chose to endure the sexual dysfunction with the understanding that it was drug related and would remit when they stopped taking the drug. This cost-versus-benefit decision enabled us to observe the subsequent spontaneous reversal of anorgasmia with continued drug treatment and positive treatment response over a prolonged period of time.

A relationship between sexual dysfunction (specifically, anorgasmia or ejaculatory failure) induced by MAOI, tricyclic, and triazolobenzodiazepine thymoleptic treatment has been established (1–3). This side effect can lead to compliance problems. Orgasm in the female is considered analogous to ejaculation in the male (2). The precise pathophysiologic mechanism of both is not understood and suffers from a lack of knowledge of the mechanisms of the human sexual response. MAOIs, tricyclics, and triazolobenzodiazepines may produce sexual dysfunction at three levels: 1) the peripheral level—through direct or indirect actions on muscarinic and adrenergic receptors of the autonomic nervous system, 2) the hormonal level—through perturbation of the hypothalamic-pituitary-gonadal axis and/or related end organ effects, and 3) the central level—through direct or indirect alteration of neurotransmitter system function. A central reciprocal mechanism in which dopamine stimulates and serotonin inhibits sexual behavior has been described (4, 5). Additionally, sexual dysfunction may result from presynaptic α-2 receptor antagonism (6).

The current literature on MAOI-associated sexual dysfunction is sparse in view of its frequency. Underreporting and lack of inquiry are contributing factors. Simpson et al. (7) suggested that it occurs in 10%–30% of patients given relatively modest doses. Wyatt et al. (8) demonstrated sexual dysfunction in five of seven subjects treated with 60–90 mg/day of phenelzine for intractable narcolepsy. Treatment of neurodermatitis with 75 mg/day of phenelzine produced orgasmic or ejaculatory incapacity in eight subjects within 4 weeks (9). Rabkin et al. (10) reported anorgasmia or impotence as the most prevalent side effect in 22% of moderately depressed patients treated with phenelzine. In depressed patients, Harrison et al. (11) demonstrated decreased sexual function in 8% of men and 16% of women given placebo, 80% of men and 57% of women treated with phenelzine, and 50% of men and 27% of women treated with imipramine. Recovery of sexual function occurred within 1–3 weeks of discontinuing medication.

Literature review (5, 7, 12–17) supports our observation that orgasmic dysfunction occurred in a delayed relationship with antidepressant response in previously treatment-resistant patients who had been free of sexual problems while taking their former medications. Furthermore, when reduction of the dose of MAOI reversed the sexual dysfunction, relapse of depression seemed to follow (7, 12–15). In our patients, raising the dose of medication back to a level where depression remitted also resulted in recurrence of orgasmic dysfunction. Efforts to relieve the anorgasmia by switching to another MAOI were not likely to have been useful (15, 18).

There are reports that a serotonin antagonist (cyproheptadine) (15, 19) or a cholinergic agonist (bethanechol or prostigmine) (1, 20) can ameliorate this medication-induced anorgasmia. However, the number of patients treated with these agents is quite small, and there have been no controlled studies.

It is possible that the spontaneous remission of the anorgasmia is an idiosyncratic finding peculiar to our patients. However, it more likely supports the thesis that such synchrony reflects an integrated shift in CNS functioning (9). The observed association between therapeutic response and the onset of suppressed orgasm suggests a potentially useful marker. The anorgasmia may indicate that an adequate antidepressant dose has been attained and prognosticate a positive treatment response. Further study and replication are necessary.

CONCLUSIONS

This study illustrates that a conservative approach can be used with patients who develop orgasmic dysfunction while taking an MAOI. Drug discontinuation or the addition of other agents may be avoided. The clinician should bear in mind that many patients will not spontaneously discuss sexual concerns and that they should be specifically asked about changes in sexual functioning. For the patient who develops sex-

ual problems, careful explanation of the meaning of the symptoms, encouragement, and support are reassuring and can reduce noncompliance. MAOI-induced anorgasmia can spontaneously remit at therapeutic levels.

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Therapeutic Effect of Sleep Deprivation in Patients With Premenstrual Syndrome

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Eight of 10 women with premenstrual depression responded to one night's total sleep deprivation and maintained their improvement after a night of recovery sleep. In responders, subsequent late-night partial sleep deprivation was more effective than early-night deprivation.
(Am J Psychiatry 1987; 144:808–810)

Total and partial sleep deprivation temporarily alleviates symptoms in a majority of patients with major depressive disorder (1). Premenstrual syndrome (late luteal phase dysphoric disorder) and affective disorders may be related illnesses (2–5). To our knowledge, the possible antidepressant effects of manipulations of the sleep-wake cycle have not been investigated in patients with premenstrual syndrome. In this pilot study, we examined the effects of total and partial sleep deprivation on the symptoms of women with premenstrual depression. We felt that the possible therapeutic effects of sleep deprivation in these patients would be of interest because 1) this would help clarify the relationship between premenstrual syndrome and major depressive disorder, 2) the effectiveness of total or partial sleep deprivation would be consistent with the current theories that implicate prolactin in the pathogenesis of premenstrual syndrome (6) inasmuch as sleep deprivation profoundly lowers prolactin levels (7, 8), and 3) sleep deprivation might prove useful in the treatment of premenstrual syndrome. With regard to this last possibility, the clinical use of sleep deprivation in major depressive disorder has been limited by the short duration of its therapeutic effect; however, in premenstrual syndrome the depressive episodes are themselves short and therefore might be treated effectively with one or several nights of partial or total sleep deprivation.

Received March 13, 1986; revised Jan. 13, 1987; accepted Feb. 20, 1987. From the Clinical Psychobiology Branch, NIMH. Address reprint requests to Dr. Wehr, Clinical Psychobiology Branch, NIMH, Bldg. 10, Rm. 4S239, 9000 Rockville Pike, Bethesda, MD 20205.

METHOD

The patients were referred from local professionals, information centers, and community groups and recruited with a newspaper advertisement requesting subjects for studies of mood and behavior changes across the menstrual cycle. The screening procedures consisted of questionnaires, a psychiatric interview, a physical examination, and laboratory tests, including SMA-12, CBC, urinalysis, and measurement of thyroid indices. If the patient had no history of major medical, gynecologic, or psychiatric illness aside from affective illness, had regular menstrual cycles, appeared to have premenstrual symptoms sufficiently severe to disrupt social or occupational functioning, and was willing to endure the rigors of a long-term research study, she was admitted to a 2-month evaluation phase. (Since we were interested in studying the relationship of premenstrual syndrome and major depressive disorder, an ongoing affective illness, although not a history of affective illness, was reason for exclusion from the study.) This evaluation consisted of twice-daily self-ratings of mood on a 100-mm visual scale, daily sleep logs, weekly mood inventories, activity monitoring with a wrist actometer, and weekly clinic visits for rating on the Hamilton Rating Scale for Depression. On the basis of these 2-month prospective measures, we subsequently studied those subjects who met the following criteria for premenstrual syndrome: 1) during the week before menses the patient met the *DSM-III* criteria for major depressive episode (excluding the requirement of a 2-week duration of symptoms), 2) the

patient's affective symptoms began and peaked during the week before menses and declined within a few days after cessation of menses, and 3) the patient's mean objective ratings were 30% higher during the week before menses than during the week afterward. At the time of the study the patients had been free of all medications for at least 2 months, except one patient who received maintenance thyroid replacement. All subjects gave informed consent to their participation in the study.

Forty patients were screened. Ten met the study criteria; their mean age was 30 years (range=26–45 years). When they began to develop affective symptoms (Hamilton score≥10) during a premenstrual phase of the cycle, they were admitted to an inpatient research unit at the National Institute of Mental Health and totally deprived of sleep for 40 hours (7:00 a.m. to 11:00 p.m. the following day). The Hamilton score, excluding items relating to sleep (items 4–6), weight (item 16), and diurnal mood variation (item 18), was obtained by a nonblind psychiatrist (B.L.P.) on the morning (7:00 to 9:00 a.m.) and evening (7:00 to 9:00 p.m.) before and after total sleep deprivation and after a recovery night's sleep in the hospital. The mean of the two ratings for each day was used in data analysis. Since many premenstrual symptoms include symptoms characteristic of atypical depressions that are not assessed by the Hamilton Rating Scale for Depression, separate items (N.E. Rosenthal et al., unpublished data) assessing fatigue, social withdrawal, and increase in appetite and carbohydrate craving (maximum of 23 points) and a hypomania rating scale were added to the Hamilton scale. In addition, the patients completed self-ratings on 100-mm visual scales every 2 hours from admission to discharge. During the night of sleep deprivation, the patients were checked every 15 minutes by nurses to ensure wakefulness.

In subsequent months five of the patients who responded to total sleep deprivation participated in a random order crossover comparison of early and late partial sleep deprivation. Early sleep deprivation involved sleeping from 2:00 to 8:00 a.m., and late sleep deprivation consisted of sleeping from 8:00 p.m. to 2:00 a.m.; the patients spent two consecutive nights in each condition. Results of previous studies of patients with major depression (9, and unpublished observations of Sack et al.) indicated that early partial sleep deprivation was ineffective and therefore might be used as a sham treatment to control for nonspecific aspects of the intervention. A therapeutic response to total or partial sleep deprivation was defined as a decrease of 5 or more points on the Hamilton scale.

RESULTS

Eight of the 10 women had decreases of 5 or more points on the Hamilton scale after total sleep deprivation. The mean±SD scores before and after sleep deprivation were 18±5 and 6±5, respectively (paired t test, two-tailed, $t=5.56$, $df=9$, $p<.0001$). For the six patients for whom ratings were obtained after a recovery night's sleep, the Hamilton score was 3±2, which was significantly different from the pretreatment score (paired t test, two-tailed, $t=8.09$, $df=5$, $p<.001$). It was not significantly different from the posttreatment score ($t=1.31$, $df=5$, n.s.). The mean±SD score on the atypical items (fatigue, carbohydrate craving, social withdrawal) before total sleep deprivation (8±5) was significantly different from the score after sleep deprivation (4±4) ($t=2.91$, $df=9$, $p<.05$) but not after recovery sleep (5±3) ($t=2.0$, $df=5$, n.s.). The difference between the atypical ratings after sleep deprivation and after recovery sleep was nonsignificant ($t=0.78$, $df=5$, n.s.). Although several patients reported feeling "high" and having increased energy and euphoria, no patient was actually rated manic. In two patients, significant further improvement occurred after the recovery night's sleep; one patient reported improvement for 6 months thereafter. The patients with (N=5) and without (N=5) prior (not current) episodes of depression responded equally well to sleep deprivation.

The five patients who received partial sleep deprivation improved greatly when it occurred in the second half of the night but very little when it occurred in the first half; the mean±SD Hamilton scores before and after late sleep deprivation were 19±3 and 7±5, respectively, and the scores before and after early sleep deprivation were 14±4 and 11±4 (paired t test on delta change from before to after late versus early sleep deprivation, $t=6.12$, $df=4$, $p<.05$). In the three women whose baseline ratings revealed protracted premenstrual symptoms (1 week or more), a follow-up Hamilton rating was done 1 week later. The one patient who responded to late sleep deprivation maintained her response (Hamilton score=1). The two patients undergoing early sleep deprivation relapsed (scores=20 and 22). There was no consistent difference in pattern of mood change across the day (morning versus evening Hamilton scores) between responders and nonresponders.

DISCUSSION

In this study, eight (80%) of 10 women with premenstrual syndrome responded to total sleep deprivation with sustained improvement in their symptoms through the remainder of the premenstrual period. This response rate is consistent with or superior to that seen in endogenous depressed patients (1) and contrasts with the dysphoric response seen in normal subjects (10).

This study shares with most other clinical investigations of therapeutic sleep deprivation a significant methodological problem: neither the raters nor the patients were blind to the procedure when the clinical assessments were made. The results of the study simply

indicate that the responses of patients with premenstrual syndrome to total sleep deprivation are similar to those of other types of depressed patients studied under similar conditions. In future studies it may be possible to control for nonspecific aspects of sleep deprivation therapy. The results of this and other studies indicate that partial sleep deprivation in the first half of the night is less effective than partial sleep deprivation in the second half of the night; therefore, early sleep deprivation may serve as a sham treatment. The favorable responses of patients with premenstrual syndrome to total sleep deprivation in the uncontrolled study and the positive response of a subgroup of those responders to late partial sleep deprivation suggest that a large-scale crossover comparison of late and early partial sleep deprivation in patients with premenstrual syndrome might be worthwhile. Furthermore, since partial deprivation is as effective as total deprivation (9), since repeated partial deprivation is more readily tolerated than repeated total deprivation, and since the duration of an untreated episode of premenstrual syndrome is short, repeated partial sleep deprivation may prove to be an effective and acceptable alternative or adjunct to the pharmacological treatment of premenstrual syndrome.

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Dementia in an American-Chinese Nursing Home Population

Michael Serby, M.D., James C.-Y. Chou, M.D., and Emile H. Franssen, M.D.

Of 58 demented residents in an American-Chinese nursing home, 44 (75.9%) had multi-infarct dementia, seven (12.1%) had possible Alzheimer's disease, four (6.9%) had other dementias, and three 5.2% had unknown disorders. Alzheimer's disease was relatively less prevalent than in U.S. nursing homes overall.

(Am J Psychiatry 1987; 144:811–812)

Alzheimer's disease is a major health problem in the United States and in all other developed countries in the world. It is a major cause of hospitalization and admission to nursing homes. Of the more than one million Americans in nursing homes, the majority have probable Alzheimer's disease (1). Despite the magnitude of this medical and social problem, the epidemiology of Alzheimer's disease has not been comprehensively studied (2).

There have been few cross-cultural studies of Alzheimer's disease. Schoenberg et al. (3) found that the prevalence of dementia (without specific diagnoses) was comparable between blacks and whites in a rural county in Mississippi. Treves et al. (4) studied presenile dementia of the Alzheimer's type in Israel and noted that the incidence was significantly higher in Ashkenazi Jews (born in Europe or North America) than in Sephardic Jews (born in Africa or Asia). Two recent studies from Japan (5, 6) reported findings suggestive of dementia patterns different from those seen in the West (1, 2). The investigators found that within the demented Japanese sample they studied, the ratio of multi-infarct dementia to Alzheimer's disease diagnoses was 2:1 to 4:1. This contrasts sharply with the generally accepted relative prevalence of 0.5:1, which is based on northern European studies (2). A recent American study (7) found a higher prevalence of multi-infarct dementia in a heterogeneous ethnic sample. In addition, there have been anecdotal reports that Alzheimer's disease is relatively uncommon among the Chinese (8, and unpublished paper of A.S. Henderson, 1982).

We have attempted to further explore the relative cross-cultural prevalences of Alzheimer's disease and multi-infarct dementia by surveying an American-Chinese nursing home population.

METHOD

We studied all 61 American-Chinese residents of a nursing home in an urban American community with a large Chinese population. They ranged in age from 59 to 100 years (mean=81.6 years); 34% were male (N=21) and 66% were female (N=40). All patients had been born in China. Their charts were reviewed for reports of mental status, diagnoses, and results of laboratory tests, including VDRL, thyroid function tests, serum B_{12} and folate measurements, EEG, CSF studies, and computerized tomography scans. All patients were interviewed and received a neurological examination. A modified Mini-Mental State was given to each patient. Two items from the standard Mini-Mental State were found to be culturally invalid and were excluded from the modified version ("no ifs, ands, or buts" and "Write a sentence" were excluded since grammar, sentence structure, and usage in Chinese are very different from English). The subject's family was contacted when the history was unclear. Diagnoses were independently determined by two psychiatrists.

The demented patients were scored on the Modified Hachinski Ischemia Scale (9); a diagnosis of multi-infarct dementia required a Hachinski score of 4 or more. The diagnosis of possible Alzheimer's disease was made according to the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, per McKhann et al. (10), and the *DSM-III* criteria for primary degenerative dementia.

RESULTS

Of the 61 American-Chinese nursing home residents, 58 were found to be demented according to

Received Aug. 6, 1986; accepted Oct. 23, 1986. From the Department of Psychiatry, New York University School of Medicine. Address reprint requests to Dr. Serby, Psychiatry Service, New York VA Medical Center, 408 First Ave., New York, NY 10010.

Supported in part by stipend funds from an APA/NIMH Minority Fellowship.

The authors thank Dr. Neal L. Cohen, Dr. Abraham Khaski, and the staff of Gouverneur Hospital's Skilled Nursing Facility for their cooperation.

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DSM-III criteria. Among the 58 demented patients, 44 were diagnosed as having multi-infarct dementia and four had dementia due to other identifiable causes. These included one patient with Parkinson's disease, one with hypothyroidism and Parkinson's disease, one with pernicious anemia, and one with an undiagnosed neurological disorder that included a peripheral neuropathy.

Among the 10 patients with dementia of unknown etiology, two had several risk factors for multi-infarct dementia but did not score enough points on the modified Hachinski Ischemia Scale to warrant a diagnosis of multi-infarct dementia. Another patient had multiple myeloma and could have been demented because of brain metastases, although we were unable to verify this.

The remaining seven patients with dementia of unknown etiology fulfilled the diagnostic criteria for possible Alzheimer's disease (10). If all of these patients did indeed have Alzheimer's disease, the ratio of multi-infarct dementia to Alzheimer's disease would be 6.3:1. If all 10 unknown dementias were Alzheimer's disease, then multi-infarct dementia would still predominate and the ratio would be 4.4:1.

DISCUSSION

Our sample had a 95% prevalence of dementia. Although this is higher than the prevalence in U.S. nursing homes overall (1), it is not surprising in view of the wide variability in admission policies. There may be many nursing homes with few if any demented patients, while other homes have virtually 100%.

Our major finding is a relative prevalence of multi-infarct dementia and Alzheimer's disease of from 4.4:1 to 6.3:1 in an American-Chinese nursing home population. This contrasts sharply with the low relative prevalence of multi-infarct dementia in American nursing homes altogether (1). These preliminary data suggest that there might be true ethnic differences in the prevalence of Alzheimer's disease and in the relative prevalences of multi-infarct dementia and Alzheimer's disease. This is consistent with epidemiologic studies of some other ethnic groups. Multi-infarct dementia is apparently more prevalent than Alzheimer's disease in Japan (5, 6). Alzheimer's disease has a significantly lower age-specific incidence in Sephardic Jews than in Ashkenazi Jews (4). These differences could be explored to determine the etiologic contributions of genetic and environmental factors in the development of Alzheimer's disease.

However, our results may have alternative explanations.

1. Diagnostic inaccuracy is always a potential pitfall in dementia workups, but it is less of a problem when patients have obvious cerebrovascular disorders.

2. Since we sampled only one nursing home, selection bias may have resulted in unrepresentative figures.

3. Further selection bias could have been caused by cultural issues, such as the extended Chinese family, which might care for its mild to moderately demented elderly at home and tolerate a high degree of cognitive dysfunction before approaching professional health care facilities. This, however, would not explain the altered proportion of organic etiologies in our sample, since Chinese families would have no reason to provide home care longer for patients with Alzheimer's disease than for patients with multi-infarct dementia.

4. The accepted estimates of the relative prevalences of multi-infarct dementia and Alzheimer's disease in the United States may actually be incorrect, as most of them were ultimately based on northern European studies.

Certainly, further studies of larger, statistically significant samples of American-Chinese, native Chinese-Americans, mainland Chinese, and non-Chinese groups are indicated. Such studies may shed light on important genetic and environmental factors in dementia.

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Naltrexone Treatment for Postconcussional Syndrome

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Two patients with postconcussional syndrome whose most severe symptoms were blackouts, headaches, and amnesia episodes appeared to respond to naltrexone. Because life-saving emergency trauma services are widely available, it is likely that the incidence of postconcussional syndrome will increase.

(Am J Psychiatry 1987; 144:813–814)

Postconcussional syndrome refers to the chronic intellectual, physical, and behavioral impairments that sometimes result from head trauma (1). The symptoms can last from months to years and may even be permanent. To date, no medical treatment has been reported to be effective. Naloxone has been shown (2, 3) to reduce the severity of experimentally induced concussive brain injury and assist memory in animals. Naltrexone, a long-acting congener of naloxone, has recently been marketed. Its duration of action ranges up to 72 hours, in contrast to only about 2 hours for naloxone, so it can be used for clinical purposes other than the treatment of acute opioid overdose (4). We report here the cases of two patients with postconcussional syndrome who did not respond to numerous other treatments but appeared to markedly improve with naltrexone.

CASE REPORTS

Case 1. Ms. A, a 28-year-old woman, fell off a stool, hit her head, and lost consciousness. Her husband and mother described her as normal before this event, and she had never received psychiatric care. On recovering consciousness, she experienced intermittent chronic blackouts, headache, amnesia, loss of balance, dissociation of thought, and inability to calculate or perform household tasks. During some periods her symptoms were so severe that she required constant monitoring by family members lest she lose consciousness or leave home and become lost. She had a normal EEG, skull X-ray, and CAT brain scan. Over 4 months she was treated with a variety of therapeutic agents, including tricyclic antidepressants, diphenylhydantoin, carbamazepine, benzodiazepines, and neuroleptics. None provided any symptomatic relief. Our evaluation of her revealed significant short-term memory loss, cognitive impairment, poor balance, positive Romberg test, bilateral presence of Babinski reflexes, and a Mini-Mental State test score of 18 (normal=27–30) (5).

She was given 0.4 mg (1 cc) of naloxone subcutaneously. Her short-term memory and balance immediately improved, and the improvement lasted about 6 hours. This procedure was repeated four times during the following week with similar results, so a trial of oral naltrexone at a dose of 100 mg/day was attempted. After 1 month of treatment, she no longer experienced blackouts, lost her balance, became disoriented, or developed total amnesia. After maintenance of this regimen for 3 months and after Ms. A gave informed consent, placebo that appeared identical to naltrexone was substituted on a single-blind basis. Within 24 hours Ms. A developed a recurrence of headache, amnesia, and disorientation, which again remitted, within 48 hours, when naltrexone treatment was resumed. On two occasions, when Ms. A failed to take a dose of naltrexone her symptoms immediately returned. At the time this article was written, she had been maintained on the naltrexone regimen for 15 months, and her Mini-Mental State test scores ranged between 25 and 27. She had almost normal short-term memory and no severe headaches, blackouts, or total amnesia episodes. Ms. A's Babinski reflexes were still present, and she continued to have a positive Romberg test. She had not lost weight, and the results of her liver function studies remained normal.

Case 2. Ms. B, a 24-year-old woman, sustained a concussion in an automobile accident approximately 6 years before our treatment. The evaluation after her accident showed normal skull X-ray, EEG, and CAT scan. She had been treated with antidepressants, anticonvulsants, and neuroleptics, which had been unsuccessful. Her family reported occasional blackouts. In addition, on most days Ms. B had episodes of garbled speech, rages of temper, loss of balance, headaches, depression, and amnesia, which prevented her from telling time, reading, writing, or performing household tasks. Her Mini-Mental State test scores on 3 different days ranged from 25 to 27.

To evaluate the possible utility of naltrexone, a double-blind clinical trial was done with the consent of Ms. B and her family. She was given a 50-mg capsule each day for 3 weeks and an identical placebo capsule for 3 weeks. The weeks were randomized so that she received naltrexone during weeks 1, 4, and 6 and placebo during the other weeks. The capsules were given to the family to administer each day, and the code was kept by a monitor who was never involved with Ms. B's clinical treatment. On the same day each week we evaluated Ms. B, and her mother reported the number of

Received July 30, 1986; revised Dec. 29, 1986; accepted Feb. 5, 1987. From the UCLA School of Public Health and UCLA Center for Health Services. Address reprint requests to Dr. Tennant, Research and Education Division, Community Health Projects, Inc., 336½ South Glendora Ave., West Covina, CA 91790.

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days during the previous week that Ms. B had experienced episodes of temper rages, amnesia, stumbling or falling, depression, and garbled speech. Her family also reported overall general improvement or decline and whether they believed she had received placebo or naltrexone that week. At the completion of the study, the family reported overall improvement and correctly identified the 3 weeks that Ms. B had received naltrexone. In addition, the family reported the following symptoms for a significantly lower proportion of days of naltrexone treatment than for placebo therapy: temper rages (19.0% versus 47.6%; $\chi^2=3.84$, df=1, $p<.05$), amnesia (42.9% versus 76.2%; $\chi^2=4.01$, df=1, $p<.05$), depression (47.6% versus 80.9%; $\chi^2=5.19$, df=1, $p<.05$), and garbled speech (47.6% versus 100%; $\chi^2=14.9$, df=1, $p<.001$). Although there were fewer reported days during naltrexone treatment on which Ms. B fell or stumbled (42.9% versus 66.7%), this was not a statistically significant difference at the $p<.05$ level. After the double-blind trial, Ms. B was maintained on 50 mg/day of naltrexone. After 10 months of treatment she had improved to the point that her family no longer reported any amnesia, blackouts, garbled speech, or falling, although temper rages and depression were occasionally observed. Ten Mini-Mental State test results during this time period all showed a score of 30, the maximum possible. The results of her liver function studies and her weight remained stable.

DISCUSSION

The incidence of postconcussional syndrome will likely increase because of the widespread availability of emergency trauma services, which facilitate life-saving transport and treatment of accident victims. Last year the National Head Injury Foundation in Framingham, Mass., reported that more than 700,000 Americans, mostly males between the ages of 16 and 25, received head injuries severe enough to require hospitalization. Of these, between 50,000 and 90,000 were estimated to suffer a variety of permanent symptoms that will prevent them from living independently again (6). The lay press has recently labeled this condition "the silent epidemic" (6).

Naltrexone was associated with improved symptoms in the two cases reported here. One patient was evaluated under single-blind rather than double-blind conditions, however, so the data here must be considered preliminary. The mechanism by which naltrexone may have been effective is unclear, but it might be related to blockage of endogenous opioids (2–4). Since no other therapeutic agent has been reported to be consistently effective for the symptoms of postconcussional syndrome, a carefully controlled clinical trial of naltrexone may be warranted.

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Book Forum

Nancy C. Andreasen, M.D., Ph.D., Editor

ETHICAL ISSUES

The Foundations of Bioethics, *by H. Tristam Engelhardt, Jr. New York, Oxford University Press, 1986, 387 pp., $27.95.*

This volume will be ranked as one of the major books published in bioethics in recent years. Written by an important contemporary figure in the field, philosopher-physician H. Tristam Engelhardt, Jr., it is his most comprehensive statement to date on the fundamentals of the discipline. There are three reasons why psychiatrists should read it. First, it is written with refreshing clarity for a philosophical treatise. Although some preliminary familiarity with moral philosophy would be helpful, philosophically untutored psychiatrists will find that all key concepts are carefully defined and the arguments lucidly developed. References are extensive and drawn from classical and modern sources, often with illuminating annotations. Second, it is simply essential that all physicians, psychiatrists included, educate themselves about the assumptions and competing theories in modern bioethics. Ethicists are calling for a fundamental rethinking of the morality of medical practice. To engage this debate intelligently will require that physicians be informed in matters of philosophical discourse. This book provides helpful insight into how modern bioethicists think, especially those within the currently dominant neo-Kantian tradition. Third, this book is important because of the vision it portrays, a vision as vast as the domain of all rational creatures in the universe and as specific as the diagnosis of disease. Here we learn about the author's views regarding the moral limits of the state's authority as well as the ethics of the physician-patient relationship.

What can one say about Engelhardt's moral vision? He begins with a disclaimer—that the book he ultimately wrote was not the one he intended to write, that he had hoped "to find grounds for establishing by reason a particular view of the good life and securing by general rational arguments the authority for its establishment. To my dismay and sorrow, such have not been available." This admission is fundamental because it sets the stage for a two-tiered ethical system. The first, the ethics of individual autonomy, is foundational—the hard, nonnegotiable core of morality. The second is the ethics of beneficence, which, since reason cannot provide its content, becomes the soft, negotiable, and ultimately irrational superstructure of aesthetic preferences.

Engelhardt is to be commended for the clarity with which he articulates his basic position and the courage he demonstrates in working through to his conclusions, even in those instances where, he warns us, they may appear radical. And some of them do. For example, he does not morally condemn infanticide, the killing of the severely demented elderly, or the prescription on demand of pharmacologic euphoriants, positions that follow quite logically from his premises. Although these conclusions may be counterintuitive, it is precisely the lack of a rational foundation for our moral intuitions, or for any alternative source of content in ethics, that drives Engelhardt to his conclusions.

Only occasionally does he lapse into inconsistency. He attempts, for example, to argue that one should not loan one's 12-gauge shotgun to a college sophomore who is despondent and suicidal because his lover has jilted him, on the grounds that it would violate "one's moral sense." But he has already conceded that our moral sense can provide no binding content for ethics. If the new formulation of the Golden Rule, "Do unto others their good," which Engelhardt endorses, is valid, then no one could be held morally accountable for providing the shotgun.

But these are mere quibbles. The more basic issue is whether Engelhardt's ethical vision can be sustained on its own terms. The answer is that it cannot, for reasons both philosophical and practical. Philosophically, Engelhardt completely separates form from content in ethics, but in creating his preferred form, that of a peaceable, secular community, he must endorse certain values over others—free choice over coercion and rationality over empathy. But it is precisely these value preferences which require justification. To attempt, as Engelhardt does, to establish these as the necessary or inescapable preconditions of access to ethical discourse is not persuasive. One simply needs to ask, "But why should I agree that such a definitional tautology merits my acceptance?" Such is the problem with every deductive morality. Its value commitments are concealed within its premises. From there, it is simply a matter of deductive reasoning.

In practice, too, Engelhardt's morality is problematic. A procedural ethic, one limited to committees, to bureaucracies, and to governments, cannot provide the good citizens necessary to its functioning. Such persons will need to be tolerant, liberal, and prudent. But procedural ethics can neither develop such citizens nor provide reasons why they should value these virtues over others. These citizens must be reared in families and communities characterized by other values and purposes. Seen from this developmental perspective, the ethics of autonomy is not foundational but, rather, derivative, even parasitic, of a communal-beneficence-based ethic.

Moreover, as psychiatrists should be forewarned, the practice of medicine—its values, its diagnoses, and its norms—all must be relegated within Engelhardt's dualism to the domain of negotiable values, indistinguishable from questions of taste or taboo. This is both a startling and unworkable vision. In such a morality, there can be no rational standard for valuing health over illness, pleasure over pain, or life over death. All such values turn out to rest on nothing more than the voluntary and irrational agreement of the parties involved and therefore can be invalidated by a majority vote. In the end, Engelhardt's procedural ethics is politics. In a liberal democracy, this ethic is reduced to the prevailing view of the majority. In other polities, it reduces to the corresponding embodiment of might makes right.

Although Engelhardt's foundations for bioethics do not hold, psychiatrists should by all means read this book. But they should not read it alone but peruse as well Alasdair

MacIntyre's *After Virtue* (1) and Leon Kass's *Toward a More Natural Science* (2). Within the terms of reference of these three books, they will find the crux of the crisis in contemporary medical morality.

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The Long Darkness: Psychological and Moral Perspectives on Nuclear Winter, *edited by Lester Grinspoon. New Haven, Conn., Yale University Press, 1986, 208 pp., $25.00; $7.95 (paper).*

Every animal and plant on this planet, from ants to antelopes and daffodils to reindeer, ought to stand up and bray, buzz, neigh, or trumpet a salute of thanks to Dr. Carl Sagan for speaking up on their behalf. Dr. Sagan is the foremost exponent of what he modestly terms "elementary planetary hygiene"; by this he means the necessity of preventing nuclear annihilation. I will not use the term "nuclear war" because it is precisely Dr. Sagan and his colleagues' invaluable work that must forever put the kibosh on any attempts to classify nuclear weapons as traditional tools of warfare. Whatever the moralists and scholasticists may argue as to the "just" nature of nuclear battle, Dr. Sagan and others have elegantly shown for any who care to see that "nuclear war" will not be just another war.

Rather, the detonation of even a small fraction of today's nuclear arsenals may result in unpredictable and synergistic ecological effects that may very well stop the process of biological evolution on this planet forever. Most people are accustomed to thinking of the effects of a single nuclear bomb as a short-term pulse of heat and blast followed by long-term radiation (that is, if most people think of this at all). Dr. Sagan's group has calculated the effects of thousands of nuclear explosions occurring virtually simultaneously all over the Northern Hemisphere and in hundreds of places in the Southern Hemisphere as well. The combination of soot, smog, and smoke and depletion of the ozone layer would probably produce a period of darkness and intense cold lasting from weeks to months or years. In combination with widespread radioactivity, nuclear winter would probably spell the death of us all and possibly the death of all of the rest of the biosphere as well.

In *The Long Darkness,* Lester Grinspoon presents Dr. Sagan's adaptation of the landmark article he wrote for *Science* in 1983 with R.P. Turco, O.B. Toon, T.P. Ackerman, and J.B. Pollack (1). This adaptation, entitled "Nuclear War and Climatic Catastrophe: Some Policy Implications," is a much more readable, comprehensible summary for the general public. Dr. Sagan's conclusions are rhythmic, congruent, and rational. If even a "successful preemptive strike" by one superpower on the other might trigger global catastrophe, surely any reasonable person would veer away from such a policy. Yet precisely the opposite is happening, at least in the United States. Even while the Soviet Union has extended a yearlong moratorium on nuclear testing and offered major concessions on arms control, the United States has accelerated testing and continued the policy of developing and deploying weapons capable of a first strike.

The rest of this book consists of efforts to understand this insanity. There are contributions by Erik H. Erikson, Jerome D. Frank, John E. Mack, and Robert Jay Lifton as well as essays by Henry Steele Commager, Stephen Jay Gould, and J. Bryan Hehir. Each article is well written, persuasive, and interesting—eminently digestible food for thought.

Yet I long for spicier fare. The possibility of nuclear winter highlights the nauseating fact that nuclear weapons represent a revolutionary change in human destructive potential. And so a similar revolution in our thinking would seem to be called for.

I am still waiting for a Gandhi or a St. Joan. I find myself disappointed that no such person has emerged. Although I wish to congratulate each of the contributors and the editor of *The Long Darkness* and to encourage them to keep up the good work, I also wish that least one woman—Helen Caldicott, Randall Foresburg, Petra Kelly, or another—had been included herein, not simply as a token feminist but because each of the aforementioned has been, in effect, a revolutionary leader. Yet, perhaps precisely for that reason, academic psychiatrists and the uncommitted should find this book palatable and, let us hope, transformational.

As adults and as custodians of this planet for all of the human children, born and unborn, and all of the species of beasts and flowers, we should all read and internalize the meanings and messages in *The Long Darkness.* Current policy makers will not be our leaders. It is our task to go beyond this book and to transmute understanding into informed action and inspired leadership.

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HISTORICAL PERSPECTIVES

Origins of Mental Illness: Temperament, Deviance and Disorder, *by Gordon Claridge. New York, Basil Blackwell, 1985, 207 pp., $45.00; $9.95 (paper).*

All efforts to integrate the plurality of theories about the essence and the genesis of mental illnesses in a unifying conception must be acclaimed. That is the case for this book, which is presented to us with the heavy title of *Origins of Mental Illness.*

The subtitle gives a hint of the viewpoint from which the book was written. That the work is dedicated to Hans Eysenck shows that the wind is blowing from a behavioristic direction. The opinions of the author, a clinical psychologist who is occupied with clinical investigations of psychiatric deviations, are many-sided and multi-shaded. This book is a refreshing alternative to the often monothetic conceptions of biological psychiatric authors. Although Claridge opts for a biological basis of behavior and aberrations, he calls himself an adversary of the people who say that mental illnesses are brain diseases in the generally accepted sense.

How is that possible? Is Claridge a mentalist, a materialist, or neither? To answer these questions I have to explain the

most important themes, in their different variations, that are treated in this book.

The author starts from the basis that behavior reveals the same degrees of variation as there are individuals. There exists a gradual and continuous transition from normal to deviant behavior, including severe psychiatric disturbances. On arbitrary grounds, a division in temperaments of the personality is made. Variations in behavior and psychological activity are manifestations of differences in the organization of the brain.

Claridge argues that biologically based temperamental characteristics are synonymous with the predestination of different forms of mental illness. In other words, in most cases people will develop the psychiatric disturbances that their temperament allows; the anxious temperament may develop a fear neurosis, the impulsive temperament a psychopathy, and the melancholic temperament a depression. I leave it to the reader to decide if this is profound wisdom or a tautology. A last theme deals with the genetic origin of the variations of temperaments, which in turn predispose to deviant behavior or mental illnesses.

Up to now this theory creates the impression of a strong deterministic tendency and a materialistic attitude. Claridge denies this suspicion with great emphasis. To buttress his denial, he makes a comparison between physical medicine and psychiatry. The first deals with abnormalities of function that are relatively localized: the patient complains of pain in the abdomen or displays tenderness or swelling in some part of his anatomy, signs that allow the possibility of disease to be recognized and understood without reference to the whole of the individual. The diagnosis can be obtained on the basis of the symptoms. On the other hand, in psychiatry the situation is quite different. There the very signs of illness are themselves behavioral or psychological. Our decision about whether a person is sick is often difficult to disentangle from judgments based on interpersonal, cultural, legal, and even political criteria. Exceptions are the psychiatric illnesses traced to gross changes in the nervous system—those caused, for example, by a tumor of the brain, lues, or anatomical anomalies of the brain. Real objective criteria for diseases as they exist in physical medicine do not exist in psychiatry.

The author's theory of temperament is based on Ivan Pavlov's ideas of nervous types. Pavlov's theory of nervous types has had a direct impact on psychology and psychiatry in Eastern Europe. Lately his ideas have started to have more influence in the Western world. Pavlov viewed the individual nervous system as a very complex constellation constantly under the control of two active but opposing processes working on all levels of the nervous system. Each individual has a relative balance of excitation and inhibition; some tend more toward excitability, and others are more easily inhibited. These neurophysiological differences appear in differences of mental activity and can be put on a continuum.

Obviously, Claridge connects this neurophysiological vision with the continuous, variable dimensions of personality: introversion, extraversion, neuroticism, and psychoticism. This division of Eysenck is completed with the idea of arousal in at least two systems—from the reticular formation to the higher nervous system and from the limbic system or "emotional brain" to other parts of the brain responsible for integrating events concerning emotion. Characteristics of temperament and curiosity are connected to neurophysiological theories. Claridge also makes an effort to integrate the newer ideas about stimuli processing and asymmetric hemisphere function with the ideas mentioned earlier in the book.

These are the most important themes that come up for discussion in this book, in each case in a different light. The variations on the themes are shown in the discussion of such important groups of psychiatric diseases as neuroses, psychoses, and borderline personality disorders.

Readers without a medical education can follow the author's technical expositions because he does not use specialized terminology. Claridge tries to integrate interactional, psychological, and neurophysiological processes. He can even appreciate the good sides of Szasz, but he rejects Szasz's well-known extremism. Claridge does not hide his antipathy to psychoanalysis, which is characterized as an exotic folklore. That is not correct, in my opinion, because I think it is possible to integrate psychoanalytic theory and the theory of biological (stimuli-processing) systems. That is a missed chance. Claridge's reintroduction to the ideas of Pavlov is refreshing and forces me to look at Russian psychiatry with a new perspective. I think it would make sense to give another, more modest title to the book in the next edition.

Claridge has made a courageous attempt to interweave biological and psychological theories. It is not surprising that he did not succeed entirely, because it is an almost inhuman task fulfilled by few people. For that a vision broader than the author demonstrates in this book is needed.

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Penicillin: Meeting the Challenge, *by Gladys L. Hobby. New Haven, Conn., Yale University Press, 1986, 319 pp., $32.50.*

The development of penicillin was one of the outstanding scientific achievements of the twentieth century. Many books have described one or another aspect, but the total picture is still far from complete. In this book Gladys Hobby, one of the pioneer American investigators, while giving a good overview of the early years, pays special attention to the period 1940 to 1945. These were indeed the crucial years, and they are described in fascinating detail.

The difficulties would seem to have been overwhelming. In the 1930s there was already considerable promise that penicillin would have clinical value, but it was hard to obtain in adequate quantities for study. Rigorous bacteriological research was needed to show the range of organisms that would be susceptible, first in vitro and then in animal experiments. Then there was always the problem of whether experimental work could be translated into clinical usefulness. Meanwhile, penicillin was in short supply, purification was difficult, and suitable assays and standardization were as yet nonexistent.

Chain and Florey and their co-workers published their first scientific report in August 1940, and within a year they showed the effectiveness of penicillin in controlling streptococcus infection in mice. The first clinical trials in patients were carried out early in 1941, with promising results.

The war strained British capacities to the utmost. Nevertheless, despite shortages in manpower and financial support as well as in physical facilities, several British investigators made remarkable progress. Hobby discusses several of the British investigators and their work, not familiar to most nonspecialized American readers. In the United States, a group at Columbia, including Dr. Hobby, had been working with penicillin since 1940; this group confirmed some of the earlier British work. In 1941 Florey and Heatley came to the United States to enlist support, and they succeeded in inter-

esting several key figures and pharmaceutical firms. The groundwork was laid for cooperation, and the great initial progress in the techniques of fermentation soon resulted in greatly increased yields of penicillin.

Dr. Hobby indicates some of the ethical as well as the technical problems faced by the early scientists. Supplies of penicillin were limited. How should the available supplies be allotted? There were three sets of conflicting demands—bacteriological research, clinical research, and actual clinical use where research had already demonstrated effectiveness. Priorities had to be set up, especially for clinical use, with consideration of civilian as well as military needs. Distribution of the scarce material had to be rigidly controlled and centralized, and the making of allotments often involved anguishing decisions.

By 1945 the battle for the large-scale production of penicillin had been won, and the story is truly a dramatic one. In parts this book reads like an engrossing novel, and abundant photographs of the principal investigators add much to the interest. However, in other parts, especially those dealing with the period after 1945, the writing is often arid and the interest flags. An author who has had a vivid firsthand experience in a crucial period of activity infuses into the writing an enthusiasm that leaves its mark on the reader. Writing that derives chiefly from secondary sources does not possess this quality.

Dr. Hobby's book is a major contribution to the history of science. It helps to round out a fascinating story.

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ECONOMICS AND EPIDEMIOLOGY

From Advocacy to Allocation: The Evolving American Health Care System, *by David Mechanic. New York, Free Press, 1986, 238 pp., $24.95; $12.95 (paper).*

As the title of this book implies, the American health care system is experiencing profound changes due to economic, political, and ethical pressures that are without precedent in our history. This extremely coherent and far-reaching book describes the essential issues we are attempting to grapple with in this era of prospective payment, entrepreneurialism, and increased regulation of medical care.

The book is superb in its capacity to describe the problem, with succinct, well-written statistical summaries of the cost and utilization of medical care. It also provides a framework of analysis and evaluation, allowing a physician to rethink many of the assumptions used to approach his or her work circumstance when it is undergoing unprecedented stress, environmental upheaval, and soul-searching.

From the perspective of the physician, the shift from advocate to allocator brings to the front the essential balancing act that we all engage in when treating patients. It is Dr. Mechanic's point that it is the community, through free public debate and governmental process, which must set the framework and financial constraints for the overall system of care. But it is the private doctor-patient relationship where the balance of advocacy and allocation becomes most critical. Implicit professional decisions and explicit trusting relationships between patients and providers should decide the individual care opportunities for us all. Dr. Mechanic clearly inveighs against excessive rules and resorting to the legal process to resolve these inevitable conflicts. He tackles many issues of current concern. These include changing role expectations for physicians, the trade-off between acute and long-term care, the needs of the elderly and the adolescent, the changing roles for nurses within the overall medical care system, social policy and mental illness (especially as such policy relates to the chronically mentally ill patient), and ethical dilemmas of high-technology medicine. Throughout, he explores the increasing unfairness of the medical care system and the disenfranchisement of the poor or near-poor from access to quality medical care and from being able to choose alternatives.

In "Public Conceptions of Medicine," a superb chapter, Dr. Mechanic articulates the view that we are living simultaneously in an era of rationing and an era of commercialization. He notes that medicine has slipped in relation to the public's priority system and that there is more support for various cost-containment initiatives, such as rate regulation, diagnosis-related groups (DRGs), preferred provider organizations (PPOs), and health maintenance organizations (HMOs). Yet the resulting ethical dilemmas in the allocation of health care services (a title for another chapter) dominate the discussion. To quote Dr. Mechanic, "It is ironic that a system of care so successful at preserving the life of a premature infant of just a few pounds, or allows continued functioning of many patients through transplantation of organs or through maintenance on the artificial kidney, does so poorly in serving the chronic mental patient, or in assisting the frail elderly in retaining sufficient function to remain in their own homes" (p. 207). It is the elaboration of this issue, combining both the clinical perspective and the policy opportunities, that makes this book so worthwhile.

Dr. Mechanic, from a behavioral and social-psychological point of view, focuses on the needs of the chronically mentally ill and on the doctor-patient relationship. Too few of our health economists and social policy makers have the breadth to encompass these issues. We are indeed fortunate to have this commentary. This is a special book and should be read by everyone, including patients, professionals, and politicians, who worries about the future of the health care system in America.

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Psychiatric Services for Underserved Rural Populations, *edited by L. Ralph Jones, M.D., and Richard R. Parlour, M.D. New York, Brunner/Mazel, 1985, 293 pp., $37.50.*

This is a remarkably good book about an important and neglected topic. The editors assembled a group of authors with practical knowledge of the problems of working in rural settings. They have achieved a degree of coherence often absent in edited works because they wrote or contributed to 11 of the 19 chapters. They set a high standard for themselves and the other contributors. Their obvious in-depth knowledge of the subject matter is evident throughout. The unifying theme is that rural areas are different from metropolitan areas demographically, socioeconomically, interpersonally, and ideologically. Understanding these differences is crucial to success for the newly arriving rural mental health practitioner.

The first of five sections, Conceptual Issues, introduces the reader to the territory. Leona Bachrach presents a sociological perspective, drawing on her experience as a member of President Carter's Commission on Mental Health. This is a

scholarly treatise, presenting extensive factual data as well as synthesis. Anthropologist Carole Hill presents an excellent chapter on folk health beliefs and practices. Her insights are valuable and have applicability for anyone working with different ethnic and cultural groups. The next two chapters, by Jones and Parlour, concern principles of designing rural psychiatric services and prevention services. Rural mental health practitioners have to be prepared to be generalists and adapt to unusual practice situations. Often, the intense stigma against mental illness and psychiatry in rural areas makes provision of mental health services within another agency more acceptable and effective. The chapter on prevention is disappointing but reflects the general state of pessimism prevalent today concerning prevention in psychiatry.

Section two, Professional Considerations, contains the most valuable reading for one contemplating rural mental health practice. This section presents administrative issues and explicates the roles of the various mental health professions. Jones and Parlour see the primary care physician as fundamental in diagnosing and treating the mental and emotional problems of rural patients. The psychiatrist is more effective as a consultant to the primary care physician than as the primary caregiver because of the stigma against psychiatry, the great distances that need to be covered, and the relative scarcity of psychiatrists willing to practice in rural areas. Thelma Mueller and Doris Williams describe how social workers enhance and aid primary care practitioners dealing with mental and emotional problems by adding their knowledge of psychosocial factors and as family and group counselors. The important role of nurses as case finders, outreach workers, caregivers, and case managers is outlined by Ethel Minsloff. She describes and advocates a broadly independent role for nurses that goes far beyond the traditional concept that many physicians may have of nursing practice. Curiously, there is no mention in this book of the role of psychologists in rural mental health. My impression is that rural psychologists are increasingly prevalent and important in independent practice and within community mental health centers.

Section three, Forensic Issues, consists of two chapters, both excellent. In rural areas the local jail is often the first place a mentally ill person may be taken, and in the absence of effective emergency services this is not inappropriate. Rural law officers know who is having emotional problems and is in need of help. Effective liaison with them is an important and appreciated part of mental health practice.

Section four, Crisis Intervention, contains five uneven chapters. The one on psychopharmacology is dated and incomplete; specifically, rapid neuroleptization is now being questioned by many practitioners, the discussion of neuroleptic malignant syndrome does not mention treatment possibilities, and there is nothing about the use of antidepressants or lithium. This latter is particularly disquieting because the evidence is that primary care physicians are among the more frequent prescribers of antidepressants, often in ineffectively cautious doses. Norman Farberow's chapter, "Disaster Management," is a superb exposition of this complex topic; he argues for increased emphasis on training for disaster management. In rural areas the response to disaster is frequently inadequate. Preparedness is a community effort that would strengthen the whole mental health network. "Emergency Psychiatric Services" by Lucy Ozarin offers descriptions of model programs and points out the difficulties of maintaining such services in rural areas and the need for innovation.

The final section, Special Populations, deals with children, the mentally retarded, and the chronically mentally ill. When usual mental health services are difficult to offer or maintain, services for special populations or problems are scarce as hen's teeth. The common message is that innovation, cooperation, and the rural social network can help to alleviate some of these problems. Families bear the greatest responsibility for caretaking and suffer most from burnout and disappointment. Obviously, the more the family is supported in their role as primary caregivers, the more successfully their needs will be met.

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Epidemiologic Field Methods in Psychiatry: The NIMH Epidemiologic Catchment Area Program, *edited by William W. Eaton and Larry G. Kessler. Orlando, Fla., Academic Press, 1985, 373 pp., $45.00.*

This edited volume of 17 chapters is a detailed description of the history and methods of the Epidemiologic Catchment Area (ECA) study of the National Institute of Mental Health (NIMH). The first of the book's six sections is a single chapter that summarizes the historical context, development, and objectives of the ECA program. Section two describes the issues related to sampling community and institutional populations and the methods used in the ECA study. The third section is a nuts-and-bolts description of the mechanics of the study. For example, there is a chapter on the training and characteristics of the field interviewers as well as a chapter on preparing and entering the data on the computer. Sections four and five focus on the cornerstone of the ECA program, the Diagnostic Interview Schedule (DIS), and the last section tackles statistical issues.

To better evaluate whether there was a need for the present volume, I reread the initial series of articles from the ECA study published in the October 1984 issue of *Archives of General Psychiatry* (1–3). The results of this uncontrolled case study suggest that the book is not critical to the appreciation and the understanding of the *Archives* articles. Not surprisingly, much of the book's information was contained in these articles. I enjoyed reading about the methodological nuances underlying sample selection, instrument design and construction, interviewer training, and data entry; however, I suspect that most readers would not be interested in such details. I would compare this book to a manual for conducting cognitive/behavior therapy for depression—it is important to read only if you are planning to conduct similar research.

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SUICIDE

Suicide, *edited by Alec Roy, M.B., B.Chir. Baltimore, Williams & Wilkins Co., 1986, 195 pp., $29.50.*

Suicide fascinates the psychiatric researcher, vexes the psychiatric clinician, and haunts the families of those who have died by suicide. Suicide is a dramatic topic of interest to all psychiatrists. This volume is designed as a resource on suicide for academic and clinical psychiatrists as well as other mental health professionals. The editor, Alec Roy, is a recognized expert in the study of suicide and has collected a series of fine authors, including Seymour Kety, Marie Åsberg, George Murphy, and Eli Robins, to bring together the magnitude of clinical issues associated with suicide. The book begins with chapters covering the epidemiology, genetics, and biological factors of suicide. The volume continues with chapters discussing suicide within the framework of individual psychiatric diagnoses, including depression, alcoholism, schizophrenia, and neurosis and personality disorder. Topics in concluding chapters include suicide in adolescents and the medically ill as well as chapters dealing with management of the suicidal patient and suicide prevention.

The authors address the issue of the gap between the current scientific research on suicide and the difficult clinical task of dealing with patients who have attempted suicide or who are contemplating suicide. Part of this problem lies in the hazards of using simple identified risk criteria on a clinical basis. An example given to illustrate this fact is that being single, widowed, or divorced are all risk factors for suicide, yet since three-fourths of the adults in the United States are married, more married people commit suicide. Thus, misunderstanding of relative risk and absolute risk can be confusing to practicing clinicians. The other statistical difficulty in determining accurate predictors of suicide has been the low base rate of suicide. With 12.5 deaths by suicide per 100,000 person years, the statistical task of developing accurate predictors is difficult. Researchers stretching for good reliability kappas on rare psychiatric diagnoses will sympathize with this prediction problem in suicide research. The authors in this volume have done an excellent job of using the statistics of suicide as a framework for dealing with clinical situations.

Edited books often overlap in some chapters, and this volume is no exception. The overlaps tend to be few and are usually on information it doesn't hurt to review from another author's perspective. References are up-to-date, and the writing is generally of high quality. One disturbing finding is an introductory chapter giving this advice to clinicians evaluating the suicidal patient: "Suicide is best understood not so much in terms of some sets of nosological boxes, e.g., depression or any of the often sterile labels in the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders,* but rather in terms of the two continua of general personality functioning: *perturbation* and *lethality*" (p. 13). This statement contradicts the design and philosophy of the book, which corresponds better to the advice of George Murphy: "Diagnosis is the key to appropriate treatment in all clinical medicine, and no less so in the recognition of suicidal risk" (p. 173) and "The great rarity of suicide in the absence of *active* major psychiatric illness shows that identification and treatment of the underlying psychiatric illness are the most direct routes to suicide prevention" (p. 178).

Norman Kreitman sums up the state of psychiatry regarding suicide by stating, "It has to be accepted that in the present stage of knowledge it is not always possible to avoid a suicidal outcome" (p. 194). This volume gets clinicians the information to make a "best effort" at preventing suicide. Unfortunately, we never have the pleasure of knowing our actions resulted directly in the prevention of a suicide, just as we are unaware of the consequence of not acting. So clinicians treating psychiatric patients can only continue to learn as much about suicide as possible and apply the principles they discover in everyday work. This book is a fine scientific and clinical volume to aid psychiatrists in this endeavor.

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EATING DISORDERS

Anorexia Nervosa and Bulimia: Diagnosis and Treatment, *edited by James E. Mitchell, M.D. Minneapolis, University of Minnesota Press, 1985, 206 pp., $25.00.*

Are we in the midst of a publishing binge in the field of eating disorders? It would seem so. A large number of books are available today for the lay public and the medical community. Early on, it seemed that people wrote a volume filled with case histories or else took a stand on some unitary explanation for bulimia or anorexia nervosa. Now, as researchers and clinicians realize that these disorders probably exist on a continuum with many etiological factors and many treatment options, we have books available that represent the eclectic views of the various treatment centers. *Anorexia Nervosa and Bulimia* is such a book. The editor, James Mitchell, presents the experience at the University of Minnesota in treating these frustrating disorders. As usual with such multiauthored books, the chapters vary in quality and style. On the whole, though, the book presents a great deal of information for the neophyte as well as for the experienced clinician.

Divided into two main sections, Diagnosis and Treatment, the book contains nine chapters covering the characteristics, medical complications, and psychodynamics of anorexia and bulimia as well as behavioral and psychopharmacological approaches to treatment. The Minneapolis group's integrated treatment programs for anorexia and bulimia are described in detail, and, as a coda, data from a recent study of adolescent attitudes and behaviors toward weight and eating are presented as well.

The most helpful and illuminating chapters in the book are Eckert's on the characteristics of anorexia nervosa and Mitchell and Pyle's on bulimia. Both chapters provide excellent reviews of these disorders, with comprehensive bibliographies. The sparser literature on bulimia is well covered and up-to-date. The chapters on medical complications and psychodynamics, while reasonably complete, offer little in the way of new insights or information. For those unfamiliar with these aspects of anorexia and bulimia, the sections could serve as a worthy introduction. However, experienced clinicians will find little that is new or startling. The bottom line regarding comprehensive treatment for both disorders seems to be try a little bit of everything—a smorgasbord of therapeutic interventions, if you will. And the result is what you'd imagine: some get cured, some get better, and some don't respond. Some day—perhaps in our clinical lifetime—we'll understand these disorders and come up with a truly definitive treatment. In the meantime, we may as well digest

these guidebooks, think critically about what we read and do, and try our best.

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Handbook of Psychotherapy for Anorexia Nervosa and Bulimia, *edited by David M. Garner and Paul E. Garfinkel. New York, Guilford Press, 1985, 572 pp., $39.50.*

This collection of articles is edited by two well-known experts in the field of eating disorders. The focus of the book is primarily on management and psychotherapeutic issues in the treatment of anorexia nervosa and bulimia.

In the first section, entitled The Context for Psychotherapy, one chapter, written by Hilde Bruch shortly before her death, provides a historical overview as well as a concise summary of her own theory of the etiology of anorexia nervosa. The second section, Psychoanalytic Approaches, includes two chapters, both of which provide viewpoints that were new to me. Alan Goodsitt, in a coherent and concise fashion, presents the theory that anorexia nervosa arises from deficits in the self rather than neurotic conflicts; he also provides specific guidelines for treatment. In "Accepting the Symptom: A Feminist Psychoanalytic Treatment of Anorexia Nervosa," Susie Orbach contributes the most controversial chapter in the book. Although Orbach presents a very interesting conceptualization of feminine psychology, the clinical data she presents are anecdotal and unproven. The most troubling aspect of this chapter is the implication that treatment can be successful without direct therapeutic confrontation of the patient's underweight status.

The third section addresses cognitive and behavioral therapies, which have been so fruitful in the treatment of both conditions. The chapter by Alyson Hall provides an interesting glimpse into the loneliness and sadness experienced by group therapists working with anorexia nervosa patients. James Mitchell and colleagues present an overview of their intensive outpatient group treatment for bulimia, which is based on an abstinence model. The fifth section, Family Therapy, is disappointing in that the authors of these chapters do not provide any data to support their very interesting anecdotal descriptions of family interactions.

The sections entitled Inpatient Treatment and Multicomponent Treatment Programs focus primarily on the management issues in treatment. The final section of the book, Support and Educative Methods, includes an outstanding chapter by Garner and colleagues on psychoeducational principles. Specific guidelines are provided for the clinician attempting to assist the patient in understanding the consequences of abnormal eating practices in a way that promotes the reuniting of the classic mind/body dichotomy which occurs in these disorders. This chapter might be helpful for patients as well as their therapists.

In summary, this is an outstanding book, although its title is misleading. It is not a handbook because several chapters present very divergent and conflicting views, and it addresses issues other than the psychotherapy of eating disorders. Nonetheless, it is a comprehensive textbook that includes a wealth of very useful information for both the experienced and inexperienced clinician.

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Reprints of Book Forum reviews are not available.

Letters to the Editor

Dr. Laufer and Colleagues Respond to a Letter About Their Article on Posttraumatic Stress Disorder

SIR: Charles Kadushin, Ph.D., and Ghislaine Boulanger, Ph.D., made three criticisms (1) of our article on distinguishing different symptom patterns in posttraumatic stress disorder among Vietnam veterans (2). First, they challenged the basic distinction we made between the reexperiencing and denial subsets of symptoms contained in the *DSM-III* specification of the disorder. Second, they argued that we drew invalid conclusions from the results of a regression analysis of symptoms on traumatic war experiences. Third, they contended that the correlation of other difficulties, such as feelings of demoralization and guilt and patterns of postservice arrests and drug use, with symptoms related to posttraumatic stress disorder probably resulted from the effect of traumatic war experiences on both, suggesting that the correlations were spurious and the result of previous war experiences. We will examine each of these criticisms in turn.

Drs. Kadushin and Boulanger argued, on the basis of a range of statistical analyses, that the symptoms we examined cannot be differentiated into more than one dimension. The fact that no factor analytic model can find dimensions in the symptoms examined does not mean that conceptual divisions, such as the one we used, cannot be examined or cannot produce fruitful results. The basis of their claim would be supported if the stability and reliability of the symptom scale were reduced by partitioning it into various components. The Cronbach alpha measure of reliability for the entire set of 17 symptoms was .72. The reliability of the subscales we constructed and based our measures on was not markedly lower, although the scales contained fewer symptoms. The coefficients were the following: for the three symptoms of intrusive imagery, .62; for the six symptoms of hyperarousal, .75; for the six symptoms of numbing, .67; and for the two symptoms of cognitive disruption, .64. These reliability coefficients indicate that we did not sacrifice the underlying stability of our symptom scale by dividing it into components that were conceptually meaningful, nor were our results based on the performance of unreliable scales.

A second comment on the reliability of our measures was made in regard to our construction of measures of exposure to and participation in episodes of abusive violence. The method by which we constructed these measures was discussed at length on page 1306 of the article; i.e., they were dichotomous measures and not scales. Of 78 positive cases there were only six cases of disagreement among the raters, and four of these cases dealt with determining whether the subject should have been properly coded as a witness to or a participant in an episode.

The second criticism concerned our analysis of the regression results. We do not claim that the analysis we performed statistically tests the difference between the effect of exposure to and the effect of participation in abusive violence. The structure of the analysis contrasted each of these groups to the group of veterans not exposed in any way, while those who participated were significantly more likely to report denial symptoms than those not exposed. The fact that the other effects in the equation were not significant indicated that the differences observed should be interpreted as random variations.

In regard to the last point, Drs. Kadushin and Boulanger failed to understand our discussion on page 1309 of the article. We examined simultaneously, in a multiple regression framework, the effects of military experiences and postservice psychological conditions and behavior patterns. We found that the relationships between current feelings of demoralization and posttraumatic stress disorder symptoms were not spurious, although the relationship between feelings of guilt and posttraumatic stress disorder symptoms was. The disappearance of the relationship with guilt feelings was due to the strong association between demoralization and guilt and not between military experiences and guilt. The important point of the discussion, however, was not that a relationship was present between other postservice traits and posttraumatic stress disorder symptoms but that the effects of war experiences persisted even when the association between postservice characteristics was controlled. For this reason the relationship of guilt and demoralization to posttraumatic stress disorder symptoms and its spuriousness is a secondary, and in this context uninteresting, issue.

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Renal Function and Lithium

SIR: The study by J. Raymond DePaulo, Jr., M.D., and associates (1) on renal function and lithium is a further important contribution to assessing the benefits and risks of long-term lithium therapy and renal function. There is now general consensus from both prospective and retrospective studies that lithium has little demonstrable effect on glomerular function. If lithium does produce renal insufficiency, perhaps secondary to an interstitial nephropathy, it would seem to be an uncommon occurrence, and any fault detected in glomerular filtration rate is small and determined more by age than duration of lithium treatment. An exception, however, is when renal damage occurs as a consequence of acute lithium toxicity. In a prospective study (2), my colleagues and I found a significant association between a history of lithium intoxication and significant decline in glomerular function.

The results of that study are consistent with those of other

prospective studies which have reported that impairment of urinary concentrating ability is not progressive in the majority of patients. A major determinant of urinary concentrating ability is the maintenance plasma lithium level (2, 3). Higher plasma lithium levels are associated with lower maximal urinary concentrating ability. This may be further compounded by concurrent administration of antipsychotic drugs. While further information is required to determine whether there is a critical plasma level in individual patients above which progressive changes in tubular function may occur, it is prudent to keep maintenance serum lithium levels at the lowest level consistent with adequate therapeutic effect.

Although extended follow-up in more patients will be necessary before any final conclusions can be drawn, careful monitoring with attention to plasma levels and avoidance of toxicity will diminish considerably any substantial risks of renal toxicity.

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Dr. DePaulo and Associates Reply

SIR: Dr. Johnson's letter is a concise and accurate summary of 10 years' research into the renal toxicity of lithium. Our data support the association of urinary concentrating ability with serum lithium levels. The link between lithium intoxication and decrements in glomerular filtration rate is widely accepted. However, we would like to draw attention to the case of a patient in whom lithium was associated with a decrement in glomerular filtration rate without lithium intoxication.

Mr. A, a 66-year-old man with frequently cycling bipolar affective disorder treated with lithium, developed a decreased glomerular filtration rate and increased serum creatinine level several months before his current hospital admission. Chronic obstructive pulmonary disease and hypertension were managed with α-methyldopa and bronchodilators. A small, stable elevation of serum creatinine was thought to be related to his hypertension. Mr. A's serum creatinine level rose from 1.6 mg/dl to 3.0 mg/dl over a 12-month period, while his lithium dose requirement fell from 1,200 to 300 mg/day. During this time he showed no stigmata of lithium intoxication or dehydration.

Despite a serum lithium level of 1.2 meq/liter, Mr. A cycled into a manic state and was admitted to the hospital. Consultation with a renal specialist indicated that lithium was the most likely cause of azotemia, so the lithium was stopped. Carbamazepine, neuroleptics, verapamil, and ECT were administered alone and in various combinations for 3 months in an unsuccessful effort to control the cycling affective disorder. The patient's serum creatinine level, however, fell to 1.8 mg/dl.

The decision was reached in consultation with Mr. A, his family, and the renal consultant to restart lithium while monitoring glomerular function. At a dose of 150 mg/day of lithium, with a serum lithium level of 0.5 meq/liter, Mr. A's serum creatinine level again rose to 2.3 mg/dl. Lithium was again discontinued, and within 10 days his serum creatinine level stabilized and then fell to 2.0 mg/dl; he was transferred to a long-stay facility while still in a mixed affective state. Over the 3½-month admission there were no signs of lithium intoxication or dehydration, but his serum creatinine values correlated highly with his serum lithium values ($r=.97$, $p<.01$).

This is the first patient for whom we have reinstituted lithium therapy, but we have seen one or two others in whom serum creatinine levels went up within months of starting lithium and returned to baseline after discontinuation. We assume that this renal response to lithium is very uncommon, and we reemphasize Dr. Johnson's conclusion that careful monitoring will diminish the risk of renal toxicity with lithium.

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Clonazepam Treatment of Adolescents With Neuroleptic-Induced Akathisia

SIR: Akathisia is a common and often severe side effect of neuroleptics; it may manifest itself subjectively as anxiety or depression and objectively as restlessness, pacing, or even unusual behaviors (1, 2). Often undiagnosed, it may affect patients' compliance with neuroleptic regimens and thus become a limiting factor to successful drug therapy of the psychoses (1). This is particularly problematic with adolescent psychotic patients, who may express serious reservations about the use of neuroleptics—often to the point of refusing to take them—to the detriment of successful long-term treatment. Aggressive treatment of akathisia is especially important for these adolescent patients.

Numerous medications have been used in the treatment of akathisia, but no single medication has been shown to be the definitive drug for this disorder. A recent report (3) of successful results with clonazepam (a benzodiazepine with anticonvulsant properties) in treating restless legs syndrome led us to consider its potential in treating neuroleptic-induced akathisia.

We report here the results of an open trial of clonazepam in a group of adolescent first-onset psychotic patients who were experiencing distressing neuroleptic-induced akathisia.

The 10 patients, six male and four female, whose mean age was 17.1 years (range=16–19 years), met criteria for the following *DSM-III* diagnoses: schizophrenia, paranoid subtype (first onset), N=8; bipolar, manic, N=1; schizoaffective-depressed, N=1. They had been treated with oral neuroleptics for at least 2 weeks and were selected for clonazepam treatment on the basis of objective and subjective evidence of akathisia. In addition to neuroleptics, nine of the 10 patients had been receiving the anticholinergic benztropine (mean dose=2.8 mg, range=2–4 mg).

All of the patients were assessed with the akathisia subscale of the Chouinard Extrapyramidal Symptom Rating Scale (4) at the end of the second week of neuroleptic treatment. The mean score at this time, before treatment with clonazepam, was 4.1 (range=3–6).

All 10 patients were treated with oral clonazepam, in addition to their neuroleptic and anticholinergic medications, at a dose of 0.5 mg/day, and the akathisia subscale was repeated after 1 week of treatment. All of the patients reported subjective improvement. Their mean posttreatment akathisia subscale score was 1.6 (range=1–3), and each patient's score went down at least 1 point on the scale (Wilcoxon matched pairs test, $p<.005$).

The results of this open clinical trial suggest that clonazepam, when added to routine antiparkinsonian medication, is an effective agent for the control of neuroleptic-induced akathisia. The etiology of neuroleptic-induced akathisia is unknown, but it may involve either peripheral or central mechanisms. Clonazepam has both central and peripheral effects (5). Centrally, it suppresses the spread of seizure activity without abolishing the seizure focus, which may be due either to a γ-aminobutyric acid (GABA) potentiation effect at both pre- and postsynaptic sites or to a direct inhibiting effect on neuronal excitability through influences on the calcium-dependent conduction of potassium ions. Clonazepam also demonstrates a muscle relaxant effect and is reported to have anxiolytic qualities. It is unclear which of these features is most responsible for its ability to ameliorate neuroleptic-induced akathisia.

Clonazepam's long half-life (24 hours) makes it an ideal single-dose preparation, and its antiakathisia effects are apparent at a low dosage. We plan to make further placebo-controlled, double-blind investigations of clonazepam and to evaluate whether tolerance to its antiakathisia effects develops with prolonged use. Thus, we hope to clarify its role in the appropriate management of akathisia.

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Seasonal Change in Aggressivity

SIR: The paper by Richard P. Michael, M.D., and Doris Zumpe, Ph.D., "An Annual Rhythm in the Battering of Women" (1), ends with an explanation that seems forced: "a temperature-related seasonal change in the aggressivity of a subset of the male population" that is either "a direct effect of the ambient temperature" or "a neuroendocrine mechanism" hardly seems to fit with different seasonal patterns of spouse abuse and child abuse.

Why not assume that when it is hot, women—in their own homes—are more skimpily clad? This rouses their husbands' sexual feelings. The subset consists of those women who are unresponsive and those husbands who then become aggressive and, possibly, jealous.

To test my hypothesis, one might study spouse abuse as a function of the presence, relative size, and temporal use of air conditioning in houses where such abuse occurs.

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Drs. Michael and Zumpe Reply

SIR: A direct effect of temperature on the behavior of the victim rather than on the behavior of the perpetrator, as proposed by Dr. Ronat, may apply in some cases. However, one would think that behavior which leads to an attack and to injury would be carefully avoided by the majority of women, and abused women are abused again and again. This being said, we should like to make the following points.

1. Many people still cling to the old view that crimes directed against women (notably rape) are caused by the victim rather than the perpetrator. We recognize that both individuals in the interaction are likely to contribute to its occurrence, but we have opted initially to propose mechanisms involving the abuser.

2. We have statistically demonstrated (1–3) the existence of three separate phenomena: annual rhythms in rapes (aggression by males toward females), annual rhythms in assaults (aggression mainly by males toward other males), and annual rhythms in spouse abuse (aggression by males toward sexual partners). The amplitude and timing of the rhythms in all three forms of violence are closely similar and appear to be related to ambient temperature. This suggests that we may be dealing with *one* phenomenon that expresses itself in different ways. Dr. Ronat's "explanation" for the rhythm in spouse abuse certainly cannot account for the rhythm in assaults. Conversely, the old favorite explanation for rape, namely, increased opportunity for contact between victim and perpetrator, cannot account for the rhythm in spouse abuse.

3. Comparative studies of numerous vertebrate species including nonhuman primates have also revealed the existence of annual rhythms in male-male and male-female aggression. Although homologies may not be involved, there are at least close analogies to be drawn, which lead to our working hypothesis involving biological as well as cultural and economic factors in certain forms of human violence. This was the purpose of our paper—to propose a working hypothesis—and not, as Dr. Ronat states, to provide an explanation. The fact that physical child abuse does not show the same type of rhythm as spouse abuse implies that the phenomena may be basically different.

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Alcohol Use in Volunteers 1 Year After a Study Requiring Alcohol Intake

SIR: Administration of beverage alcohol to experimental subjects may raise ethical questions, particularly when it is done for more than a few days. One potential harmful effect to be considered is that a subject might develop abusive drinking after this exposure. In the only other study published on this problem, Faillace et al. (1) found that 15 hospitalized alcoholic patients who participated in a study which involved daily drinking for an average of 2 weeks actually had a better 6-month outcome than a control group who did not drink while in the hospital.

We asked 12 volunteers (seven men and five women) from a study of the effects of beverage alcohol in the P-450 enzyme system in the liver (2) about their drinking habits 1 year after completion of the study. All subjects were friends or colleagues of the investigators. None had been known to have a drinking problem at the time of the original study, although this was not ascertained systematically. For the original study, all subjects were abstinent from alcohol for 1 month, then drank 45 g of ethanol (in 3 oz. of vodka) daily for 35 days.

A research assistant (who was previously unknown to the subjects and who was not involved in the first study) asked them a series of questions by telephone interview. They were assured that data on individuals would not be available to the original investigators. They were asked about their frequency, quantity, and type of beverage use for the preceding month and for the month preceding the original study 1 year earlier. They were also asked whether, for the year preceding the study or in the year following the study, they or anyone they knew had been concerned about their drinking and whether they had had problems resulting from their use of alcohol or had received treatment for drinking problems.

Overall drinking patterns and frequency of excessive use changed little from the month before the study to a year later. The frequency of drinking was as follows: abstinent, no subjects before the study and none after; once a month, one subject before and none after; once a week, four subjects before and five after; two or three times a week, four before and five after; four or five times a week, one before and one after; six or seven times a week, two before and one after. The numbers of occasions per month on which subjects consumed more than five drinks were as follows: no occasions, six subjects before and five after the study; one occasion, two subjects before and three after; two occasions, two before and none after; three occasions, none before and one after; four occasions, three before and one after; more than four occasions, none before and one after. One subject reported greater excessive and overall use currently, which he ascribed to a recent move. No subjects reported major problems from drinking or treatment for them. One subject reported concern about his drinking both before and after the study. There were no sex differences in overall or excessive use. One subject reported "losing his taste for booze" as a result of the study.

A study that required moderate alcohol consumption for 35 days appears to have affected these 12 "normal" control subjects very little. The recent increase in drinking reported by one subject corresponded in time with a geographic move, which he considered to be the reason for the increase. Limitations of this pilot study include the use of self-report without corroboration, the retrospective reconstruction of drinking habits, and the lack of a systematic evaluation of drinking before the original study. While this may limit our conclusions about subtle changes in drinking frequencies, the lack of problems reported by these subjects suggests that research involving intake of alcohol may be done safely. More systematic, prospective study of this question is still needed.

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Polypharmacy

SIR: I was surprised to find that under the rubric of "polypharmacy" the *Oxford English Dictionary* quotes only disparaging comments, one as early as 1762. At the present time, psychiatrists who prescribe more than two medications simultaneously often find themselves criticized by colleagues and nurses in hospitals, and they may find themselves charged with malpractice.

There can be no question that optimal practice requires that we use as few chemical agents for the treatment of illness as possible—and at the lowest effective dose possible. However, I am writing to support the thesis that many patients fail to respond to one or two drugs and require a number of chemical agents that act synergistically. Other patients are not able to accept an adequate dose of any one agent, so two or more, at low doses, have to be prescribed together. Some psychotic patients require the combination of tranquilizer and antidepressant medication. Many patients respond fairly well to properly targeted tranquilizers or antidepressants or both but still require an antianxiety drug to control residual anxiety or a sedative for residual insomnia.

In general, it is the antidepressants that are likely to fail to accomplish their purpose. For resistant patients, one may have to prescribe both a monoamine oxidase inhibitor and a tricyclic, and sometimes these must be combined with one or more adjuvants such as lithium, L-tryptophan, triiodothyronine, or one of the stimulants such as methylphenidate or pemoline. If anticholinergic side effects become intolerable, bethanechol may be required. If orthostatic hypotension is induced, fludrocortisone may become necessary. If a schizophrenic or borderline patient is depressed, a phenothiazine or thioxanthene or butyrophenone may be indicated in combination with the antidepression mixture. With sufficient resourcefulness, one may treat successfully many of the patients who resist any single drug.

I think it should be made clear in our literature that the rational combination of therapeutic agents for resistant patients represents better, rather than worse, medical practice and that a multiplicity of drugs does not in itself demonstrate malpractice.

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Estrogen-Progesterone Combination: Another Mood Stabilizer?

SIR: We report two cases of patients with bipolar disorder resistant to lithium and/or tryptophan who demonstrated a stabilization of mood with the addition of estrogen and progesterone.

Ms. A, a 56-year-old married housewife with a family history of bipolar illness, had suffered recurrent episodes of depression since the age of 53. Initially, she was treated successfully with tricyclic antidepressants, which, when abruptly terminated, appeared to induce a withdrawal mania. After 1 month, the mania responded to lithium and haloperidol. Premarin, 1.25 mg—which had been prescribed for her since a surgical sterilization that well preceded the psychiatric disorder—was continued. However, 3 weeks later a depression occurred, which responded only when Ovral (0.5 mg of norgestrel and 50 μg of ethinyl estradiol), one tablet daily, was added to the lithium, L-tryptophan, and Premarin. One month later Premarin was discontinued. Remission persisted for 5 more months until Ovral was replaced by Minovral (0.15 mg of norgestrel and 30 μg of ethinyl estradiol), lowering the progesterone levels. A new depressive episode started. As only a slight improvement was achieved with reinstitution of Ovral, medroxyprogesterone, 5 mg/day was prescribed. Since the addition of medroxyprogesterone, Ms. A has been in remission.

Ms. B, a 49-year-old widowed executive with a family history of bipolar disorder, suffered her first depression at age 42; it responded to amitriptyline. When she stopped the antidepressant abruptly, she developed cyclic mood changes. Although lithium, 300 mg q.i.d., and L-tryptophan, 3 g q.i.d., were prescribed with success for several years, the patient had a recurrence of depression. Ovral, one tablet a day, and haloperidol were added. The depression remitted and the haloperidol was discontinued. Ms. B remained well for 2 months, and then she inadvertently began to use inactive Ovral inserts 1 week of every month and manifested depressive features. However, when Ovral was prescribed on a daily basis, she became euthymic for 18 months. Ovral was then replaced by Premarin, 1.25 mg/day, which meant that she no longer received the progesterone she had been receiving. This precipitated a manic episode, which was treated with clonazepam, lithium, tryptophan, and Ovral daily. Milder cycling continued until medroxyprogesterone, 5 mg/day, was added; Ms. B then achieved a remission.

After an initial satisfactory response to lithium and tryptophan, these patients developed resistant cycles requiring different drug combinations. A euthymic state was achieved with the addition of hormones, allowing termination of neuroleptics and tricyclic antidepressants.

The mechanism of mood stabilization is unknown but may involve noradrenergic, dopaminergic, and/or serotonergic systems. Estrogen, administered chronically, increases dopaminergic receptor density (1) and decreases dopaminergic concentration in the limbic structures (2), while progesterone inhibits reuptake of serotonin and decreases its metabolism, resulting in enhanced serotonergic activity in the CNS. Chronic estrogen treatment also increases progesterone receptors in target organs, possibly augmenting the activity of progesterone in the CNS. Thus, the modulation of mood appears to be mediated through progesterone. These cases suggest that hormones may be effective as mood stabilizers in bipolar patients resistant to standard treatments.

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Research Diagnostic Problems

SIR: Making an accurate research diagnosis is frequently a complex task. We present a case that illustrates the importance of taking an extensive sexual history, obtaining collateral information when possible, and critically evaluating diagnostic data in a consensus group.

Mr. A, a 28-year-old divorced, self-employed white man, was referred to our research diagnostic team with concurrent clinical diagnoses of panic disorder and type II bipolar affective disorder, euthymic. His panic attacks had begun spontaneously at age 18. These attacks were characterized by a sense of impending doom, shortness of breath, tachycardia, diaphoresis, nausea, and numbness. His symptoms had waxed and waned over the 10-year course of illness, but during times of stress, panic attacks had exceeded one per week for more than 3 consecutive weeks.

Mr. A had been given a working diagnosis of type II bipolar affective disorder by a psychiatrist whom he had seen briefly after a marital separation when the patient was 27. In a structured psychiatric interview that used the Schedule for Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) (1), Mr. A answered affirmatively questions concerning racing thoughts, agitation, increased energy, decreased sleep, grandiosity, irritability, weight change, and financial irresponsibility during the time after the separation. He had been treated briefly with lithium carbonate, but he had discontinued the medication after 2 weeks and had changed psychiatrists.

Initial Research Diagnostic Criteria (RDC) (2) diagnoses of panic disorder, definite, and bipolar affective disorder, definite, in remission, were made. However, the consensus group was uncertain of the validity of these diagnoses. Consequently, collateral medical records were requested

and the referring psychiatrist was recontacted. After a series of consultations with the referring psychiatrist, new information came to light. Mr. A did indeed have panic attacks, but he also had a very histrionic manner and tended to answer affirmatively most questions concerning mood and affective symptoms. In addition, he started talking about his problems with sexual identification and his ongoing attempts to enter a sex-change program. A second consensus meeting was held, and our diagnoses changed to panic disorder, definite, and RDC "other" diagnoses: transsexualism, heterosexual, and histrionic personality disorder.

This case reminded us of the importance of gathering extensive supplemental history about research subjects in addition to that elicited by the SADS-L interview. It also reinforced for us the importance of carefully evaluating each subject in an experienced consensus group. We hope this case report will serve as a reminder of possible complications one might encounter in using the SADS-L as part of a research diagnostic evaluation.

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Chronic Posttraumatic Stress Disorder

SIR: Clinicians making outreach efforts to traumatized populations have reported difficulty in contacting and engaging chronic posttraumatic stress disorder patients (1). In a private practice office setting, it has been reported that as chronicity increases the dropout rate increases, ultimately reaching 81.8% (2). Chronic posttraumatic stress disorder patients in the civilian sector are elusive in the health care system. Questions such as how they fare remain unexplored.

It is understandable that patients with acute posttraumatic stress disorder would be found on the general medical floors of a hospital. It was striking, then, when I realized that a substantial proportion of my consultations relating to posttraumatic stress disorder were for elusive, chronic posttraumatic stress disorder patients. The following is a description of that patient group and the reasons the consultations were sought. Once alerted, both clinicians and researchers can further identify and explore this possible subgroup of posttraumatic stress disorder patients.

From the records of consultations done in three community hospitals over a period of several years, 43 patients were identified as meeting the *DSM-III* criteria for posttraumatic stress disorder. Twenty-two (51.2%) of these patients were chronic, according to *DSM-III* criteria. Their mean age was 36.45 years; nine were men and 13 were women. The mean time interval from the trauma until the psychiatric consultation was 174.68 weeks (range=28–500 weeks). The stressors were motor vehicle accidents (N=9), sudden losses (N=7), and other (N=6). The mean score on the Impact of Event Scale (3), a self-report instrument that measures posttrauma symptoms, was 53.9. The reasons for the consultations were as follows: conversion disorders (N=6), suicide gestures (N=5), dissociative disorder (N=1), and alcohol withdrawal delirium (N=1). In these cases, the reason for the consultation was the primary reason for admission. In the remaining nine cases, the reason for the consultation was the attending physician's concern about a concurrent mood disorder in the patient. This disorder was never identified specifically as posttraumatic stress disorder by the attending physician. In 14 (63.6%) of these 22 patients a psychosocial stressor, usually involving the loss of support of a close family member, immediately preceded the hospitalization. Eleven of the 22 (50%) reported a history of prior psychiatric treatment from a variety of sources, while only five of them (22.7%) were currently in treatment.

Study of these patients suggests that a substantial portion of posttraumatic stress disorder consultations in a general hospital will involve chronic posttraumatic stress disorder. Careful history taking is required, however, to identify these patients, since often a history of posttraumatic stress disorder is not spontaneously offered and/or other symptoms obscure or distract from the posttraumatic stress disorder symptoms. This subgroup of chronic posttraumatic stress disorder patients was not faring well. Since the maximum possible score on the Impact of Event Scale is 75, the reported score of 53.9 represents a high level of posttrauma distress. Despite this level of distress, 17 of the 22 patients (77.3%) either had never entered treatment or had dropped out.

Difficulty in modulating aggression and abuse of alcohol or drugs have been associated with posttraumatic stress disorder (*DSM-III*, pp. 236–238). However, in general, the extent to which the chronic posttraumatic stress disorder process contributed to these hospitalizations is a crucial but poorly understood area that needs future research.

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Priapism Associated With Concurrent Use of Thioridazine and Metoclopramide

SIR: A number of drugs (antihypertensives, antipsychotics, antidepressants) can produce either impotence or priapism. It has been known for many years that chlorpromazine, thioridazine, and fluphenazine can induce impotence, but reports of priapism associated with their use are more recent (1–3). Metoclopramide, a dopamine antagonist generally used as an antiemetic, is also known to cause impotence, but no reports are available suggesting the potential for priapism

with its use. We observed a case of severe priapism, of 5 days' duration, that developed after concurrent administration of thioridazine and metoclopramide in a patient with sickle cell traits.

Mr. A, a 30-year-old black man with a history of chronic paranoid schizophrenia, developed priapism within 24 hours of starting thioridazine, 150 mg/day, and metoclopramide, 30 mg/day, in divided doses. He had initially been seen in a general medicine clinic and had been given metoclopramide for a complaint of burning epigastric pain, attributed by the physician to gastroesophageal reflux. Thioridazine was initiated to treat the exacerbation of delusional ideation that had occurred since Mr. A had discontinued his previous use of the same medication.

After initiation of these medications, Mr. A developed a painfully unremitting erection and came to the emergency room for treatment. He denied a history of trauma, intercourse, or masturbation and stated that the erection had occurred nocturnally but had persisted. He denied a personal or family history of sickle cell disease and gave no history of previous priapism. Physical evaluation confirmed the erection, and laboratory evaluation showed the presence of the sickle cell trait by sodium metabisulfite sickle cell preparation.

An exchange transfusion of 3 units of blood was performed, reducing the amount of sickle cell hemoglobin to 31% by electrophoresis. With this procedure and concomitant intravenous hydration, there was a reduction of approximately 10% in the erection over several hours, suggesting that the priapism was not directly related to the sickle cell trait (4).

An incidental finding was the presence of a 13-cm wire—noted on chest X-ray and confirmed by ultrasound—perforating the right and left heart ventricles. When confronted with this finding, Mr. A stated that he had originally inserted the guitar wire subcutaneously into the left supraclavicular fossa in an attempt to use an acupuncture method for controlling anxiety and tension. He had had no pain in the approximately 5 weeks during which he could palpate the wire, but he then began to have the burning sensation as the wire started to migrate and became "lost" in his chest.

This life-threatening condition was treated surgically (requiring court-ordered temporary guardianship), and the wire was removed by means of an open median sternotomy. The priapism was essentially unchanged during this procedure. The patient's psychosis was treated with haloperidol, 5 mg t.i.d.; diphenhydramine, 50 mg t.i.d., was used as anticholinergic agent. Detumescence continued in the hospital over the course of 5 postoperative days.

While the etiology of the priapism in this case is clearly multifactorial, we feel that the dopaminergic blocking effect of thioridazine might have been potentiated by that of metoclopramide. Metoclopramide, structurally related to sulpiride, is a centrally acting dopamine antagonist that shares with other antipsychotic drugs various extrapyramidal side effects, mainly of the dystonic type. Exhibiting only weak antipsychotic effect, metoclopramide's clinical use is limited to its antiemetic properties. Metoclopramide can be compared with prochlorperazine, which is extensively used in obstetrics as an antiemetic compound (5). The possibility that the dopamine-blocking effect of thioridazine was potentiated by the concurrent use of metoclopramide may provide an explanation for Mr. A's development of priapism after administration of such a low dose of both drugs. Therefore, concurrent use of metoclopramide with phenothiazines, haloperidol, and tricyclic antidepressants should be considered with great caution, if at all.

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Defining "Depression"

SIR: Gary Rodin, M.D., and Karen Voshart, B.Sc., are to be congratulated on their overview of depression in the medically ill (1). However, the article, and virtually all the previous studies referred to in it, fail to grapple with a fundamental difficulty, which is, of course, the definition of the amorphous term "depression." The word is variously used to cover a wide variety of states of misery: grief at loss, low self-esteem, the acedia of disillusion, frustration at failed aspiration, and the demoralization of prolonged handicap or painful or mortal illness. There is also a state that is fundamentally biogenic and well recognized in its severe (psychiatric) form but poorly defined in milder degree (2). All these states, and many more, are lumped together under the single term "depression," and much clinical and research effort is then expended on defining the correlates and the treatment of the "condition." *DSM-III* defines major depression on the basis of the presence of a number of symptoms. Its authors refer to a study proposing to exclude anorexia and fatigue from this list, but most of the other symptoms in the list (insomnia, retardation, thoughts of death, and depressed mood itself) could be direct expressions of physical illness and be present without the need to postulate the presence of a depressive disorder.

Advances will not occur in this confused area until psychiatrists are able to offer clear guidelines on the recognition of the biogenic state of mild depression and its distinction from all other states of misery. Some years ago Klein (3) put forward the concept of endogenomorphic depression in an attempt to distinguish the biogenic mood disorder; the distinguishing feature of this state is anhedonia. Unfortunately, this promising lead has not received the attention it deserves, and psychiatrists have continued to be content to define a state called "depression" by a heterogeneous collection of symptoms. Recently a senior physician informed my colleagues and me that a lot of unhappy people attended his clinic, and he asked for guidance as to who among them might be helped by antidepressant drugs. The result of our

attempt to aid him was the Hospital Anxiety and Depression (HAD) Scale (4). This is a brief self-assessment scale that provides two independent subscales, depression and anxiety; the items composing the subscales are constructed from symptoms that are unlikely to be those of the physical illness itself and represent the milder (nonpsychotic) states likely to occur in nonpsychiatric settings. The depression subscale is virtually an anhedonia scale; five of the seven items reflect that state. The scale is printed in full in the original article and may be copied free of charge, subject to acknowledgment of the source and name of the scale on each copy. It is available in a great number of translations: virtually all major European and many Asian languages, including Arabic and Japanese.

Clinicians and researchers who are interested in trying to shed more light on this area may wish to know of the existence of this instrument.

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DR. R.P. SNAITH
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Dr. Rodin and Ms. Voshart Reply

SIR: We agree with Dr. Snaith that the term "depression" is confusing because it has been used to describe such a broad spectrum of clinical and nonclinical conditions. We have also emphasized the difficulty in diagnosing major depression in the medically ill. We have referred to the value of self-report screening instruments but also noted their limitations in the diagnosis of major depression.

Klein's hypothesis that anhedonia is the distinguishing feature of endogenous depression is appealing, particularly with respect to the medically ill, although the specificity and exclusivity of this characteristic in major depression have not been established. Young et al. (1) suggested that there are both vegetative and anhedonic subtypes of melancholia. Clarke et al. (2) supported the association of anhedonia with depression but suggested that it may be a "characterological marker for individuals predisposed to endogenomorphic or melancholic depressive states." We have found anhedonia to be a distinguishing feature of major depression in dialysis patients, although it was also present in about 12% of dialysis patients without this diagnosis (unpublished data).

We agree that clinically significant depressive syndromes need to be distinguished from milder depressive states. The presence or absence of vegetative symptoms, even in the medically ill, may help in making this distinction. Although some vegetative symptoms are produced by the specific effects of physical illnesses, other somatic symptoms retain their diagnostic specificity for major depression (3). Also, as Bielski and Friedel (4) noted, vegetative symptoms such as anorexia, weight loss, insomnia, and psychomotor disturbances are predictive of the response to antidepressant medication. Excluding vegetative symptoms may result in the underdiagnosis and undertreatment of major depression.

Self-rating scales of depression have been used for diverse purposes, such as evaluating the severity of depressive symptoms, screening for clinically significant depressive syndromes, and assessing the quality of life. The usefulness of any particular scale must be evaluated in terms of the specific purpose for which it is intended. When the purpose is to screen for clinically significant depressive syndromes, structured diagnostic interviews and/or the response to antidepressant treatment remain the standard by which screening measures must be validated.

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Stress and Psychiatric Training

SIR: The article by Kathryn Kris, M.D., on distress precipitated by psychiatric training (1) was a useful contribution to clarifying the stresses of the psychiatry clinical clerkship that lead medical students to seek psychiatric consultation for themselves. While it may have been omitted because it was not directly relevant to the focus of the paper, because of the implications it would have been helpful to know what steps were taken with the teachers whom the author identified as having "transgressed ethical boundaries in teaching" and caused their students sufficiently severe anxiety or depression to warrant seeking help from the student health service.

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Insurance Coverage of Mental Health Care

SIR: The increasing discrimination against mental health care in the benefits provided by insurance companies, which was described by Jo Brady and associates in their article (1), may be driven by a perception that coverage for psychiatric disorders is largely superfluous. Such a perspective was conveyed in a recent article in the *Wall Street Journal* that pointed out how utilization of psychiatric services increased with liberalization of benefits (2). The historical concentration of psychiatric attention on the relatively well-functioning, paying "worried-well" patient provides some just basis for such attitudes toward arbitrary limits on benefits. If parity with other medical benefits is not possible, a rational

means of providing for needed services while accommodating the cost-containment pressures in our society might be to have a variable copayment model determined by the severity of impairment and, perhaps, by the intensity and likely efficacy of appropriate treatment for a given patient. The well-functioning patient involved in therapy that is largely oriented toward personal growth would (appropriately) be expected to pay a large part of the cost of treatment, whereas the disabled or dysfunctional patient would be subsidized for most of whatever course of treatment was indicated. An initial evaluation and peer review of the needed level of treatment might be reimbursed fully for all insured. Organized psychiatry may be the only force in our society with the expertise to develop such a system for rational and equitable mental health coverage, which would likely be endorsed by consumer groups and, hence, ultimately by third-party payers. It is to be hoped that peer review efforts currently under way will lead to such sensible, recognized standards and that insurers will adhere to them.

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Hemodialysis in Schizophrenia

SIR: I write to express my appreciation of the overview of hallucinations by Ghazi Asaad, M.D., and Bruce Shapiro, M.D. (1). Concerning hallucinations in nonmorbid conditions, my two favorite sources are the preface to Bernard Shaw's play *Saint Joan* and Erik Erikson's biography of Martin Luther, *Young Man Luther: A Study in Psychoanalysis and History.*

I regret that the authors cited reports of reducing hallucinations in schizophrenia by hemodialysis without citing the controlled studies, including that of Wagemaker et al., that have decidedly failed to support the contention of the therapeutic efficacy of hemodialysis in schizophrenia (2–4).

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WILLIAM T. CARPENTER, JR., M.D.
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SIR: In their article on hallucinations, Drs. Asaad and Shapiro wrote that "Wagemaker and Cade ... suggested that schizophrenic symptoms decreased after hemodialysis therapy" (p. 1094). This is misleading.

Schulz et al. (1) failed to find any benefit of hemodialysis in eight schizophrenic patients. Carpenter et al. (2) studied the efficacy of hemodialysis in 15 schizophrenic patients and found no treatment effect. Vanherweghem et al. (3) conducted a study of 18 schizophrenic patients and found no benefit of hemodialysis. All three studies were done under double-blind, controlled conditions and compared active hemodialysis with sham hemodialysis.

In summary, well controlled investigations have produced no evidence that would support the use of hemodialysis in the treatment of the symptoms of schizophrenia.

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Drs. Asaad and Shapiro Reply

SIR: We thank Dr. Carpenter and Dr. Frankenburg for their letters about the reference to hemodialysis in our paper. We are quite aware that hemodialysis has never been documented as an effective treatment modality for schizophrenic symptoms, and we join Drs. Carpenter and Frankenburg in clarifying this point. However, in the treatment section of our review, we, as authors of an overview article, felt that it was important to present all treatment modalities that had been reported in the literature to be useful in the treatment of hallucinations, as concluded by the authors referred to in the paper. It is rather disappointing that Dr. Frankenburg has interpreted our inclusion of hemodialysis in the treatment section as misleading, since our intention was only to be as complete as possible in our overview.

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Right-Hemisphere Deficit Syndrome in Children

SIR: In her article "Right-Hemisphere Deficit Syndrome in Children" (1), Kytja K.S. Voeller, M.D., reported on an interesting group of children with a variety of deficits that she linked to right-side brain pathology. The children's symptoms (poor eye contact, social isolation or withdrawal, being considered weird by peers, socially inappropriate behaviors, egocentric thinking and expressive language, oppositional behaviors, atypical speech patterns, rocking, and hyperactivity) and their poor response to psychotherapy were all suggestive of "atypical" children discussed by Levine and myself (paper presented at the 30th annual meeting of the American Academy of Child Psychiatry, 1983) as a relatively common group having pervasive developmental disorders and by Cohen et al. (2) as following a developmental course parallel to that of the pervasive developmental disorders. The latter children appeared to have language

disorders that were ostensibly absent in Dr. Voeller's group. However, some (e.g., patients 2, 9, 10, and 15) of the children Dr. Voeller studied might have had a subtle language disorder, and it would have been interesting to have had these children formally evaluated for signs and symptoms of a language disorder.

One suspects that—just like the "atypical" children Levine and I discussed and the "multiplex" children described by Cohen et al.—the brain-damaged children described by Dr. Voeller constituted a group of not well understood children whose incidence and prevalence warrant much more in the way of research to clarify diagnosis, prognosis, and effective treatment alternatives.

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SIR: In her stimulating article, Dr. Voeller described 15 children with behavioral disturbances, characteristic neuropsychological profiles, and neurological findings consistent with right-hemisphere dysfunction. Almost all of the children had attention deficit disorder.

It would be interesting to know in more detail the nature of the family history of psychiatric disorder as well as the severity of the dysphoric mood disturbance in the children described. Akiskal et al. (1) described subsyndromal affective disorders emerging in latency-age children with a strong family history of major mood disorder. Could some of these children in fact have been manifesting such an early mood disorder, and would they show a more appropriate clinical response to tricyclic antidepressants?

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Neuroleptic Malignant Syndrome

SIR: The recent article by Harrison G. Pope, Jr., M.D., and colleagues (1) represents an important attempt to demonstrate that the rarity of the neuroleptic malignant syndrome depends largely on how hard one looks.

In a parallel situation, a syndrome mimicking neuroleptic malignant syndrome has recently been well documented in patients with Parkinson's disease who are treated with L-dopa. It has occurred as an adverse effect of an L-dopa drug holiday (2) and also as an "on-off" effect (2, 3). At a recent meeting on Parkinson's disease, several prominent authorities speculated that this syndrome is more common than popularly believed and is simply going unrecognized. These Parkinson's patients share many features with another population at risk: the older, often demented residents of nursing homes, who frequently receive neuroleptics. These groups of patients have chronic illnesses and are easily subject to pneumonia and urinary infections, both of which often cause a decline in function that might easily be confused with neuroleptic malignant syndrome. How frequently this occurs in either population is anybody's guess and will be impossible to estimate with techniques similar to those used by Dr. Pope and associates.

The important point of the paper—that neuroleptic malignant syndrome is underrecognized—remains, but it should not be directed only to psychiatrists. Psychiatrists probably prescribe fewer neuroleptics at nursing homes than internists do, and psychiatrists are not usually involved in the care of Parkinson's disease patients. Moreover, psychiatric outpatients who develop fever are usually evaluated for this by nonpsychiatrists. The recognition of neuroleptic malignant syndrome is important and sometimes lifesaving. All physicians—especially those who treat patients at risk—should be aware of it.

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JOSEPH H. FRIEDMAN, M.D.
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SIR: I read with interest the paper by Pope et al. on neuroleptic malignant syndrome. The authors assessed the frequency of the syndrome in a large psychiatric patient population and concluded that it may be more common than previously thought.

Neuroleptic malignant syndrome has been of clinical concern for the last 25 years. However, the reports primarily describe the signs, the presumed pathophysiology, and the pharmacological agents that are believed to cause it. The etiological role of the psychiatric disorder treated, or primary diagnosis, has generally not been considered.

There is evidence that patients with affective disorders have a propensity to develop neuroleptic malignant syndrome or severe side effects from neuroleptic drugs, while those with definite schizophrenia tolerate the drugs well (1). Even with the tendency to overdiagnose schizophrenia (2), many anecdotal case presentations of severe neuroleptic side effects have described patients suffering from disorders with affective features (3–5). Indeed, seven of the eight patients the authors described had a primary diagnosis of an affective disorder. The only patient with schizophrenia showed prominent confusion, a sign more frequently found in affective psychoses.

Thus, the authors' data further strengthen the view that affective disorders predispose to a malignant reaction to neuroleptics. Besides some interesting theoretical implications, an obvious conclusion can be drawn: to prevent this essentially iatrogenic complication, the use of neuroleptics, especially the potent ones, should be avoided in patients with suspected affective disorders. Lithium salts, antidepressants, propranolol, clonazepam, and other benzodiazepines are just some of the nonneuroleptic agents that may be effective in

treating psychotic or agitated affective states. If the use of neuroleptics cannot be circumvented, phenothiazines of the aliphatic or piperidine groups, such as chlorpromazine or thioridazine, appear to have a lesser potential for inducing neuroleptic malignant syndrome (1).

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So-Called Borderline Children

SIR: We disagree with the conclusions of Deborah A. Greenman, M.D., and associates on the issue of borderline personality disorder in prepubertal children (1) and take the liberty of criticizing some of the methods the authors used.

Hospitalized subjects were chosen for the study because they "had either threatened or attempted suicide" or, alternatively, because they had not. We are given no further criteria for inclusion, yet the children are described as a "selected sample." What were the selection criteria? In what dimensions were these subjects representative of the larger group of hospitalized children at McLean Hospital?

With respect to the method of retrospective interview (i.e., chart review), the correlation coefficient is not necessarily a good index of reliability. In the face of a high number of negative items and dichotomous scoring (yes/no), Cohen's kappa would be the appropriate statistic. Further, a high total reliability score may be inflated by certain items that are clearly defined (poor school attendance, running away, suicidal behavior), while items that are central to the authors' hypothesis may have low reliability. It is preferable to report individual item reliability in a study like this, especially when ambiguous or overly broad items are included (e.g., "manipulative/devaluing/argumentative/sadistic"; "demanding/dependent/entitled").

There is no evidence that the subjects received a comprehensive developmental evaluation or that the authors incorporated this information into the patients' diagnostic formulation. Developmental language handicaps, for example, are by no means uncommon in children hospitalized on a psychiatric service (2). A child's developmental state will necessarily influence the clinical presentation (for example, his or her performance in a play interview or in projective testing).

The authors concluded that the "syndrome of adult borderline personality disorder (is) highly prevalent in a selected sample of hospitalized children"—a syndrome characterized, that is, by "psychotic" performance on projective testing, demanding and manipulative behavior, aggression, depression, hyperactivity, and "conventional social presentation." Does this really resemble the adult borderline personality disorder syndrome? Further, elements associated with the latter, like maternal separation, family history, and abnormal EEG, did not characterize the pediatric "borderline" subjects.

What the authors have done is a chart review of a group of hospitalized children. They imposed a set of "diagnostic criteria" and then discovered that some additional items differentiated group A from group B. These items described a group of severely disturbed children, with delinquent behavior, hyperactivity, poor social skills, poor test performance, and a past history of abuse. Group A was, therefore, different from group B.

Now for the inferential leap: borderline personality disorder occurring in childhood was not only validated (in "a particularly tough test"), but the disorder was also "highly prevalent." These are not reasonable conclusions at all. For the first, it would be necessary to demonstrate clinical elements *external* to the defining criteria that not only distinguished group A from group B but also supported an a priori hypothesis about what a child with borderline personality disorder might be like. For the second, the prevalence of borderline personality disorder, one would require a better idea of how the sample was selected and how representative that sample actually was.

It is our clinical opinion that true borderline children in this age group (6–12 years) are comparatively rare and that the "borderline" label is sometimes improperly used to describe children with multiple handicaps—temperamental, cognitive, social, and familial. Their deficits are not well described by any single diagnostic term, and their treatment is best oriented around specific areas of deficit, not around a theoretical label.

Borderline personality disorder in children is neither descriptive nor prescriptive. In fact, the label may carry with it some untoward consequences for the child, as we have described (3).

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Dr. Greenman and Associates Reply

SIR: Drs. Gualtieri and Van Bourgondien raise some important questions about the methodology of our study, but unfortunately they seem to have misunderstood both the intent of the study and our discussion of the results.

Drs. Gualtieri and Van Bourgondien question three aspects of the methodology: the apparent use of correlations for the reliability of the retrospective chart review ratings, the criteria for selection of the sample, and the developmental status of the subjects. They are quite right that kappa should be used for dichotomous scoring, and we did in fact

do so. The article gave the interrater reliability as r=.83. It should have said K (kappa)=.83. We thank them for pointing out our manuscript error. We did not, however, calculate individual kappas for each item; we agree that this would have added to the credibility of the method. The paper did describe selection criteria in detail. All of the children in the study had received neurologic examinations, psychological testing, and a detailed cognitive/behavioral assessment. We are not aware that the subjects had any developmental handicaps that interfered with our ability to rate them on the study variables.

The intent of the study was to clarify the meaning of the term "borderline disorder of childhood" by looking for the prevalence of criteria for adult borderline personality disorder in a selected sample of hospitalized children. Drs. Gualtieri and Van Bourgondien apparently view us as "imposing" an arbitrary set of "diagnostic criteria." The diagnostic criteria we used were the criteria from the validated Diagnostic Interview for Borderlines. Hyperactivity was not one of these diagnostic variables; it was an independent variable. We looked for and compared the prevalence of a history of hyperactivity in the groups defined as borderline and nonborderline by the adult borderline criteria.

Drs. Gualtieri and Van Bourgondien suggest that we claimed to have validated the syndrome of borderline personality disorder in childhood and called it highly prevalent. We did not. We provided retrospective chart review evidence that a group of hospitalized children can be identified who fulfill adult criteria for borderline personality disorder. This group did not seem sufficiently different from the group of hospitalized children who did not fulfill the criteria for us to conclude that the adult criteria for borderline personality disorder define a meaningful child syndrome. The quotation about prevalence is misleading. The sentence reads, "This study showed the syndrome of *adult* borderline personality disorder to be highly prevalent in a *selected sample* of hospitalized children" (italics ours).

Finally, Drs. Gualtieri and Van Bourgondien argue against what they erroneously interpret as our advocating the use of the borderline personality disorder diagnosis for children. They call the diagnosis "neither descriptive nor prescriptive" yet write that "true borderline children in this age group . . . are comparatively rare." It is not clear what it means to speak of "true borderline children." It was to clarify the meaning and usefulness of the term that we undertook our study. We concluded, "A more discriminating method for identifying borderline children is still needed for this diagnosis to carry much meaning."

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Complications of the Surgical Treatment of Obesity

SIR: In their review of surgical methods of weight reduction (1), Albert J. Stunkard, M.D., and his colleagues maintained that gastric operations "are surprisingly safe" and exhibit "a virtual absence of long-term complications." However, such optimism may not be justified. For each variant of weight loss surgery, the number and rate of complications are roughly proportional to the number of years the operation has been in use. Vertical banded gastroplasty was introduced in 1982 and has the fewest reported complications of any weight loss procedure, as Dr. Stunkard and his colleagues pointed out (1). However, this operation may be associated with a high rate of gastric outlet obstruction: 22% of patients followed 1 year or more developed this complication (2). In one series, 24% of the patients had to be rehospitalized for intractable vomiting, and 10% were rehospitalized twice (a complete reference list and other material are available from me on request). Furthermore, vertical banded gastroplasty patients suffer high incidences of riboflavin deficiency (54%), accumulation of uric acid crystals in the urine (35%), wound infection (10%), ventral hernia (6%), and massive leaking from the stomach (1%) (references available on request). Additional follow-up will undoubtedly reveal other sequelae.

Aside from possible dangers, vertical banded gastroplasty is not as effective as other weight-reducing operations (2–4). After a 2-year mean follow-up, 69% of the patients in one report had only fair or poor results, having failed either to lose a substantial amount of weight or to maintain a loss (2). In a separate study, the failure rate was 76% after 30 months of follow-up (3). It appears premature to conclude that vertical banded gastroplasty is both safe and effective.

In addition to the complications already documented, it may be anticipated that sequelae common to other forms of gastroplasty will also follow vertical banded gastroplasty. These are short-term (hypoxemia, atelectasis, pneumonia) as well as long-term (staple disruption, ulceration, reoperation, persistent vomiting) (4). Metabolic complications include deficiencies in folate, iron, thiamine, riboflavin, and potassium, and there have been case reports of acute partial blindness, liver failure, thrombocytopenia, and acquired immune deficiency as well (references available on request). Potentially lethal cardiac arrhythmias have also been reported following gastroplasty. Severe and even fatal neurological complications have been described, including Wernicke's encephalopathy, peripheral neuropathy, and a novel syndrome characterized by ataxia and demyelinating polyneuropathy (references available on request). Disturbingly, a recent review noted that "our impression from 'corridor talk' at meetings is that the problem may be more frequent than is commonly appreciated" (4). Subtler neurological syndromes could even be commonplace; to my knowledge, no prospective neurological evaluation of gastroplasty patients has been reported.

Surgical side effects appear to have little bearing on patients' satisfaction. Over 40% of gastroplasty patients responding to a questionnaire spontaneously stated, "This is the best thing that ever happened to me," or words to that effect, even though 52% of these patients suffered abdominal pain and 77% admitted to problems with vomiting (5). Gastroplasty patients have undertaken great risk, suffering, and expense to lose weight. The positive reports elicited after weight loss surgery may sometimes reflect cognitive dissonance or denial rather than a positive psychological outcome.

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Dr. Stunkard and Associates Reply

SIR: Accompanying Dr. Ernsberger's letter was a pamphlet by him which asserts that "weight loss surgery has probably killed more than 100 times as many people as the toxic shock syndrome. . . . More Americans have died from the surgeons' War on Fat than died in the Vietnam War." This hyperbole helps to explain the tactics used by Dr. Ernsberger in considering the literature on surgical treatment of obesity.

More than 100,000 persons have undergone gastric surgery for obesity, and it has been the topic of more than 400 papers. This vast literature provides abundant opportunity for an author to simply cite the highest rate of any "complication" that can be found in any study, and it appears that this is what Dr. Ernsberger has done. He lists so many "complications" that it is impossible to assess them all in a letter, but his discussion of the one that he cites most frequently—vomiting—is instructive.

Vomiting not infrequently follows gastric restriction surgery, which limits food intake by establishing a small gastric reservoir and a narrow stoma for egress of gastric contents. This outcome requires a delicate balance between a stoma that is too large and insufficiently restricts food intake and one that is too small and provokes vomiting. Even with an optimum stoma, postoperative vomiting may occur until the patient learns to adjust to a smaller food intake.

Dr. Ernsberger cites a paper with the highest rate of vomiting yet reported: 77% (his reference 5). He does not, however, mention the demonstration in our article that retrospective reports (such as this one) greatly exaggerate the rate of vomiting. Vomiting may result from stomal obstruction, and again Dr. Ernsberger selects a paper (his reference 2) with probably the highest rate of late stomal obstruction yet reported: 22%, or 22 times the 1% that was recently reported in a far larger series of patients (1). Even with respect to the paper that he cites, Dr. Ernsberger neglects to mention that endoscopic dilation controlled the stomal obstruction in the seven patients (of 32) in whom the obstruction occurred and that no obstruction was encountered in 25 other patients who were followed for shorter periods of time. Finally, the two cases of Wernicke's encephalopathy cited as "complications" pose problems of interpretation: each followed severe vomiting that went untreated for several weeks (1). The original report did not indicate why the patients' vomiting was permitted to persist or why thiamine was not administered earlier. Citation of this unusual and poorly explained outcome seems primarily a debating point.

Dr. Ernsberger does not mention the reason for the surgical treatment of morbid obesity: its very serious risk and the lack of effective conservative (medical) treatment. As just one example, the mortality of morbidly obese young men is 12 times that of men of normal weight (2).

Dr. Ernsberger agrees with the major finding of our review: patients reported favorable psychological and social consequences of surgery for morbid obesity. His dismissal of these reports is consistent with the bias in his discussion of complications.

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The Changing Presentation of Catatonia

SIR: In discussing the "*DSM-III* Implications of the Diagnoses of Catatonia and Bipolar Disorder" (1), Richard K. Ries, M.D., proposed that catatonia be classified into both schizophrenic and bipolar categories in view of the more modern diagnostic definitions. We concur with his reasoning but urge that a typological recasting of catatonia encompass an updated appraisal of its phenomenology as well.

We suggest that the traditional catatonic presentation may have undergone some transformation. It has been observed that the diagnosis of catatonia has been on the decline since the advent of neuroleptics, but this reduced incidence has not been shared by Third World countries, where neuroleptics are less available (2). Our recent studies of positive and negative syndromes in schizophrenia suggest that catatonia, rather than being less prevalent, may assume a different symptom profile in patients who undergo early neuroleptic intervention.

In a survey of 134 schizophrenic patients diagnosed according to *DSM-III* criteria, none of whom could be classified as catatonic, we found that during the acute phase a typical negative syndrome (blunted affect, poor rapport, passive social withdrawal, etc.) was associated with catatonic phenomena, such as mannerisms and posturing, negativism, disturbance of volition, disorientation, preoccupation, expressive immobility, and motor inhibition (3). Contrary to expectation from the literature on chronic schizophrenia, patients in the acute stage with a pronounced negative rather than positive syndrome were distingished by genealogical markers of good prognosis, i.e., absence of familial psychosis. These findings are compatible with the traditional assumption that the catatonic subtype of schizophrenia has a good prognosis.

The implication of favorable portent for a negative syndrome in the acute stage was borne out by a prospective longitudinal study of young acutely ill schizophrenic patients with a history of illness lasting up to 2 years (4). A negative presentation at index admission anticipated a favorable outcome at 2-year follow-up, as measured by independent clinical scales, psychometric tests, and actual days of subsequent hospitalization. In relation to other outcome predictors, including premorbid history and prior course of illness, a negative profile was a more robust prognosticator and provided a statistically independent source of prediction (5). Further analysis of our data revealed considerable overlap between the early negative syndrome and both depressive and catatonic features, which in either case could impede social, verbal, and motor functions. Such covariation, how-

ever, did not obtain after the acute phase, at which point a negative syndrome connoted greater incidence of familial psychosis, lesser incidence of familial affective disorder, premorbid cognitive developmental failures, and more severe psychopathology ratings (3, 4, 6).

We propose, therefore, that a reconsideration of the diagnostic place of catatonia include recognition of its possible new guise as a negative, deficit-ridden syndrome in young schizophrenic patients in the acute stage with early exposure to neuroleptics.

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Dr. Ries Replies

SIR: I appreciate the work of Dr. Kay and associates in helping to elucidate positive and negative symptoms in schizophrenia. However, I caution against making the inferential leaps that they have proposed. First, to show that traditional catatonic presentation of schizophrenia has undergone a transformation into a negative, deficit-ridden syndrome in young acutely ill schizophrenic patients with early exposure to neuroleptics, as suggested by Dr. Kay and his colleagues, would require a well-controlled prospective study. This hypothesis cannot be proved by association, as they have attempted.

Second, while neuroleptics may, and probably do, affect catatonic syndromes (and in fact may at times aggravate them), making conclusions from international studies is much more complex than noting the availability of neuroleptics, as is nicely discussed by Westermeyer (1). For example, using figures from reference 2 of Dr. Kay and colleagues' letter, I note that catatonia is roughly one-half as common in Western countries as in the Third World. However, the same reference reports paranoid schizophrenia to be twice as common in Western countries. Does this mean that early neuroleptic intervention in Western countries causes 1) fewer catatonic patients (with better prognosis), 2) more paranoid patients (with worse prognosis), and 3) an overall worse prognosis for schizophrenia, since studies (2) indicate a better prognosis for schizophrenia in Third World countries?

I believe that Dr. Kay and his associates have generated a nice hypothesis and backed its further study with good research; however, it is too early to adopt the conclusions proposed in their letter.

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Mental Illness in Jerusalem

SIR: We read with great interest the report by Michael Rahav, Ph.D., and associates, "Distribution of Treated Mental Illness in the Neighborhoods of Jerusalem" (1). In particular we noted and would like to comment on the higher reported prevalence of inpatient mental illness among the Ultra-Orthodox Jews of Jerusalem.

Before setting up a mental health clinic within the Albert Einstein College of Medicine's Department of Psychiatry that was geared toward the Orthodox Jewish community, we collected preliminary needs assessment data (2, 3, and manuscript in preparation). Our questioning of Orthodox and non-Orthodox mental health professionals and Orthodox rabbis, as well as our own clinical experience, suggests that another important factor may have influenced the authors' findings vis-à-vis the Ultra-Orthodox Jewish community. Orthodox Jews have a long history of distancing themselves from secular mental health professionals (3). There is considerable denial of psychiatric problems and the need for treatment. We believe this is one factor in our findings of important unmet mental health needs in this population (2, 3). Treatment is sought only as a last resort, after problems have become quite serious and more difficult to treat (4). Thus, the higher inpatient prevalence rate found for Ultra-Orthodox Jews may reflect a lack of aggressive outpatient psychiatric treatment, which might have prevented some of these hospitalizations from occurring. This would seem to hold true for a decompensating schizophrenic patient as well as for a patient who has an affective disorder that is in its early stages.

In our questioning of Orthodox mental health professionals (manuscript in preparation), their responses indicated that they did not feel that Orthodox Jewish patients had a greater frequency of severe psychiatric illness than their non-Orthodox counterparts, although this approach—distributing questionnaires to key informants—has definite limitations. Ideally, the use of a number of information-gathering techniques, including a community survey, would most accurately assess the prevalence of mental illness in a population.

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SIR: Dr. Rahav and associates' interesting paper brings forward the opportunity to discuss the question of ethical reporting in the psychiatric literature, especially in relation to epidemiologic studies that take place in areas involved in political conflicts.

I would like to discuss two conceptual flaws in the study and raise a question on the editorial review process. First, the title implies that the populations of the neighborhoods of Jerusalem were involved in data collection. The text, meanwhile, referred only to one segment of the population of the city. Considering the history of the conflict surrounding that region, one cannot but notice how the name of the whole city was used when the authors were referring to only one section of it. The title is misleading, since it does not accurately reflect the subjects in question. With it, the other inhabitants of the city do not exist; they are simply seen as non-entities. Indeed, there was no mention of how the role of the other populations as a research variable was dealt with or how the distribution of their treated mental illness compared with that of the study subjects.

Second, using the ethnicity of a given group as a basis for considering them advantaged or disadvantaged makes an unusual assumption. Being disadvantaged usually stems from political or economic factors; racial or ethnic background alone has no innate tendency toward being disadvantaged. I wonder whether the authors used ethnicity as a euphemism for economic or political factors that may have contributed to the disadvantage.

Despite its growing importance, the topic of ethics in psychiatric reporting has received little attention. Keeping in mind the variability of ethical issues and standards from one group to another (1), I wonder about the objectivity of research involving populations that are in conflict. In the light of the upcoming International Congress on Peer Review in Biomedical Publication, sponsored by the American Medical Association, in the spring of 1989 (2), what policy should editors adopt in the review process and publication of such important papers? How could the ethics of objective reporting of research findings be adequately ensured?

I would like to suggest that psychiatric studies dealing with populations in conflict be scrutinized particularly carefully, so that psychiatric literature will continue to maintain its highest ethical standards.

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Dr. Rahav and Colleagues Reply

SIR: Drs. Feinberg and Feinberg's suggested interpretation of our finding of a higher prevalence of inpatient mental illness in the Ultra-Orthodox neighborhoods of Jerusalem merits consideration. Had the study taken place in the United States, their explanation might well be more plausible than ours. However, since in Jewish Jerusalem in 1977 outpatient services or any other alternatives to inpatient treatment services were minimal (1), the "lack of aggressive outpatient treatment" was universally the case. Furthermore, Feinberg and Feinberg's belief that for Ultra-Orthodox Jews, "treatment is sought only as a last resort, after problems have become quite serious" probably holds for Israeli society in general. We have reported elsewhere (2, 3) that negative opinions about mental illness and, consequently, reluctance to use psychiatric help were common and widespread among Israelis, particularly those with little education. A disinclination to seek care, however, was not unique to the Ultra-Orthodox but occurred also in poorly educated people in secular neighborhoods, which also had very high rates of treated mental illness. Thus, in Israel the segment of the population with treated mental illness "consists only of people with problems severe enough to warrant their admission into inpatient psychiatric facilities" (p. 1250). What was unique to the highly religious neighborhood in the study we reported in this journal was the high relative risk of hospitalization for Ashkenazim. We continue to believe that a genetic hypothesis to explain these findings is plausible, although further study is called for.

Regarding Dr. Daghestani's letter, we explicitly stated that our study included only the Jewish part of Jerusalem, and we reminded readers that the city had been divided after the 1967 war into Arab and Jewish parts. We assumed equal accessibility and availability of inpatient services and similar attitudes regarding service utilization as characteristics of the mental health system in the Jewish neighborhoods. If the Arab neighborhoods had been included in the research design, these assumptions would not have held because of differences in both availability and utilization of psychiatric services. This limitation would have confounded our assessment of the relative strength of the social selection and social causation hypotheses, an assessment which, we believe, can be generalized beyond the specific Jewish setting of this study. In sum, our rationale for not including the Arab neighborhoods in our study design was methodologic, not political.

It appears that Dr. Daghestani overlooked a paragraph in our article that clearly defined what we meant by ethnic advantage and disadvantage: "Sephardim are considered to be more socially disadvantaged than Ashkenazim. . . . This social disadvantage is manifested in the lower social prestige, . . . disproportionately smaller representation in high political offices, the army, and the economy, and in their lesser accessibility to material resources" (p. 1250). Differential distribution of social advantage (prestige, power, and wealth) according to ethnic lines was not treated by us as "a euphemism" but, rather, as an objective empirical observation, based on hard data from various social indicators and a large body of literature on the association between ethnic status and social class (4, 5).

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Empiricism and *DSM-III*

SIR: The article by David Faust, Ph.D., and Richard A Miner, M.D., "The Empiricist and His New Clothes: *DSM-III* in Perspective" (1), deserves more than casual comment and respect. It presented a comprehensive examination and critique of the methodological doctrine of "strict" empiricism underlying the programmatic goals of *DSM-III*. In its aim for objectivity, the approach taken in *DSM-III* is to define disorders according to descriptive clinical features, with minimal inference, and to be "atheoretical" with regard to etiology and pathophysiological process.

The authors made it clear that the appearance of objectivity in *DSM-III* is largely illusory. They found *DSM-III* to be "replete with presuppositions and theoretical assumptions," as exemplified by its seemingly arbitrary selections of criteria for defining disorders and for categorizing descriptive clinical data.

Insofar as conceptual inference and theoretical development are considered the prime movers of scientific progress in defining and ordering data, it is easy to agree that *DSM-III*'s emphasis on description and its devaluation of (updated) inference and theory take psychiatric diagnostics back to "earlier and now revised views of science."

Such regression threatens scientific progress in psychiatric medicine on all fronts. Research impetus to test and revise current concepts and theory will be discouraged, education with regard to ongoing concepts and theory of dynamic factors underlying symptom development will be obviated, psychotherapeutic method and technique will be drastically limited in scope, and a holistic approach in examining and treating patients will be lost.

Oncoming generations of psychiatrists-in-training for accreditation will have gained knowledge about the application of objective methods for "curing" a psychiatric patient's symptoms per se, and the patient will become dehumanized.

Should the extant *DSM-III* doctrine continue as a teaching mandate without basic methodological revision, the integrity of psychiatric medicine in the United States could be compromised for decades to come—if not destroyed.

The medical director of the American Psychiatric Association voiced the economically pragmatic theory that *DSM-III*'s empirical doctrine indicates that psychiatry is undergoing maturation to "the adult stage" of its historical development. Applying the metaphor conversely, I suggest that the *DSM-III* doctrine indicates that psychiatry is undergoing not an enforced regression to its infancy but, rather, an adult progression to degenerative dementia.

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SIR: *DSM-III* indeed tends to presuppose empiricism, as Drs. Faust and Miner contended in their article. These authors then proceeded to criticize *DSM-III* by setting forth the limitations of Baconian empiricism. However, their criticism is analogous to critiques of present-day psychoanalysis that focus on Freud's original position. Empiricism, after all, has a 300-year history of vigorous change and development. We think, therefore, that it is more instructive to examine *DSM-III* from the vantage point of contemporary versions of empiricism, such as the logical empiricism of C.G. Hempel and R. Carnap.

Fortunately, Hempel himself was once invited by the American Psychopathological Association to criticize psychiatric classification (in 1959, midway between *DSM-I* and *DSM-II*). Hempel's masterful presentation is a classic in the philosophical literature (1, 2). Today we can note that it reads like a manifesto for *DSM-III*, with its advocacy of a descriptive approach that remains close to observable data, values reliability, and operationalizes terminology.

Hempel's empiricism, however, is more difficult for Dr. Faust and Dr. Miner to dismiss than Bacon's. First, these authors claimed that Baconian empiricism has no room for theory and inference. But modern-day logical empiricism certainly welcomes theories and inferences! In fact, Hempel claimed that we can never understand particular things and events scientifically unless we are able to explain or predict them through general laws and theories (1, pp 146–151). Second, since Bacon never anticipated operationalism, Drs. Faust and Miner had nothing to say about this major innovation of *DSM-III*, but Hempel vigorously promoted operational definitions for psychiatric concepts (1, 2).

How, then, should we judge modern versions of empiricism such as Hempel's? Here we firmly agree with Dr. Faust and Dr. Miner that there *are* philosophies of science other than empiricism. Elsewhere, we have tried to show the relevance to psychiatry of these alternatives (3–5), but psychiatry does in general appear to be moving toward an empiricistic monism, as illustrated by the whole project of *DSM-III* (or by the more recently proposed treatment manual). Past disagreements in psychiatry have thus been overcome by applying an "empiricist" yardstick. But doing so involves ignoring alternative—and equally defensible—methodological yardsticks. In actuality, the reigning solution is Procrustean: honest diversity is silenced by an "academy" that dictates "the one true" scientific method.

What is to be done? Thirty years ago, we were wise enough to invite outstanding outsiders such as Hempel to advise us about our methods, but no longer. Now, groups like the *DSM-III* task force do without advice from the Hempels of the present day. This is an oversight. We have become mired in narrow and outdated views of science. To escape from this predicament, future efforts like *DSM-III* should involve the broadest consultation with outstanding individuals from philosophy and the social sciences.

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SIR: "The Empiricist and His New Clothes: *DSM-III* in Perspective" includes, in my opinion, dangerous epistemological errors.

Strict empiricism is Berkeley's, Mach's, and Wittgenstein's doctrine, according to which only terms reducible to elementary sensations can be accepted in science. *DSM-III* is not built on these grounds. It accepts both dispositional ("sensitive" etc.) and theoretical ("mind" etc.) terms.

There are many empirical bases from which to argue that a system on which people agree has greater inherent scientific validity if the system is close enough to ordinary language and everyday life, and there are many more bases from which to argue that a system on which *scientists* agree has greater inherent scientific validity. According to Kuhn (1), this is the best criterion for considering empirical theories as scientific.

Facts are not theory neutral, it is true. "Fact" comes from the Latin *facere,* which means "to make." Facts are *made.* Theory A is compared with facts *a, b,* . . .; *a, b,* . . . are not atheoretical but pretheoretical data. In other words, they can be identified and verified apart from theory A, not apart from *any* theory. In this sense, relative to theory A they are objective. Theory A closely links facts *a, b,* . . . together and, in general, with available knowledge. It does so smartly, economically, and powerfully from a heuristic point of view. Theory A may eventually explain *a, b,* . . ., but it does not create them. The theoretical facts φ, ψ, . . ., which have been "created" by theory A can be used afterward to confirm theory B, but never to confirm theory A. There is a logical order of theoretical levels. Einstein's theory of relativity was experimentally confirmed by three *facts* (the shifting toward red of spectral lines in a gravitational field, the anomalies of movement of Mercury's perihelion, the bending of a ray of light). The first two "details" had already been identified before Einstein's theory; the third was foreseen by Einstein and experimentally verified afterward. All three of them retain their objectivity apart from the theory of relativity, and they could perhaps be explained in other ways.

It may be claimed that facts are built by decisions, but we cannot forget that decisions in science are made mostly on the grounds of available evidence and that many "decisions" are not of one's own free will: neither Ptolemy nor Copernicus nor anybody else could have made any personal decision about what must be considered the sun, the earth, the planets, and so on.

Theoretical inference is always epistemologically legitimate but can be accepted only if scientifically successful. *DSM-III* includes trustworthy high-order inferences (see chapter 2). Unfortunately, nowadays psychiatry enjoys few trustworthy high-order inferences. Philosophical arguments cannot modify this state of things.

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Dr. Faust Replies

SIR: First, Dr. Strahl may agree with Dr. Miner and me more than we do ourselves. Even if the relation is merely implied, it is somewhat disconcerting to find such terms as "objective" placed in potential opposition to "dehumanizing." Let us not confuse tough-minded with tenderhearted. Second, Drs. Schwartz and Wiggins and Dr. Raja articulate variants of what is often termed "sophisticated empiricism."

Dr. Raja claims that we have made dangerous errors, but we believe we have correctly articulated points that sophisticated empiricists often consider dangerous. For example, Dr. Raja claims that "there are many empirical bases" from which to argue for the greater validity of a system on which scientists agree, citing the first edition of Kuhn's book to support his statement. Aside from the fact that Kuhn backtracked considerably in the second, more recent edition of his book (1) (where he admits that disagreements about fundamental issues can occur within well advanced scientific communities), we believe Kuhn would agree that the argument is backward. It is not that a system on which scientists agree has greater scientific validity but, rather, that scientists are more likely to agree on theories of greater validity. Empiricists never locate the mechanisms of quality control within the judgment of the scientific community but instead continue to search for the nonexistent "empirical" bedrock. Further, although Dr. Raja notes that scientific decisions are constrained by the data (one should hope so), these constraints are much less restrictive than the statement suggests. As previously noted, theories with substantial supportive evidence may be abandoned for theories with very little supportive evidence on the basis of what is essentially a promissory note. Interpretation and choice of theory are constrained by rational-psychological factors that include data as grist for the mill. Advance often does reconstruct our view of the world. Copernicus did not make a personal decision about what was to be considered the sun; however, he did make a scientifically responsible but revolutionary "decision" to redefine the center of the universe.

Hempel's sophisticated empiricism leaves many fundamental issues unresolved or confused. His brand of operationalism creates more problems than it solves (e.g., if one follows Hempel, one should assume that two different ways of measuring the same thing measure different things or create unique constructs). Nevertheless, we agree that Hempel and Carnap have worthwhile things to say, and we hope that our differences with Drs. Schwartz and Wiggins reflect the type of healthy diversity that we agree is critical to scientific development. Indeed, one of these writers' concerns bears repeating: "Honest diversity is silenced by an 'academy' that dictates 'the one true' scientific method." If our paper has done something to stimulate thinking about alternative approaches to classification, we will have succeeded beyond our expectations.

REFERENCE

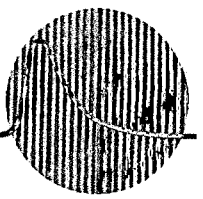
1. Kuhn TS: The Structure of Scientific Revolutions, 2nd ed. Chicago, University of Chicago Press, 1970

DAVID FAUST, PH.D.
Providence, R.I.

Reprints of Letters to the Editor are not available.

Halcion® 0.25 mg Tablets

triazolam C-IV



Helps Meet Both Goals Of Insomnia Therapy

Improved Sleep



Daytime Alertness

- *Rapidly Absorbed*
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Please see adjacent page for brief summary of prescribing information

Halcion® Tablets
(triazolam) Ⓒ

INDICATIONS AND USAGE: HALCION Tablets are indicated in the short-term management of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings, and/or early morning awakenings.

It is recommended that HALCION not be prescribed in quantities exceeding a one-month supply.

CONTRAINDICATIONS: Patients with known hypersensitivity to this drug or other benzodiazepines.

HALCION is contraindicated in pregnant women due to potential fetal damage. Patients likely to become pregnant while receiving HALCION should be warned of the potential risk to the fetus.

WARNINGS: Overdosage may occur at four times the maximum recommended therapeutic dose. Patients should be cautioned not to exceed prescribed dosage.

Because of its depressant CNS effects, patients should be cautioned against engaging in hazardous occupations requiring complete mental alertness and also about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Anterograde amnesia and paradoxical reactions have been reported with HALCION and some other benzodiazepines.

PRECAUTIONS: *General:* In elderly and/or debilitated patients, treatment should be initiated at 0.125 mg to decrease the possibility of development of oversedation, dizziness, or impaired coordination. Caution should be exercised in patients with signs or symptoms of depression which could be intensified by hypnotic drugs. Suicidal tendencies and intentional overdosage is more common in these patients. The usual precautions should be observed in patients with impaired renal or hepatic function and chronic pulmonary insufficiency. *Information for Patients:* Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing prescribed dosage, (e) possible worsening of sleep after discontinuing HALCION. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistaminics, ethanol, and other CNS depressants. Pharmacokinetic interactions of benzodiazepines with other drugs have been reported, e.g., coadministration with either cimetidine or erythromycin reduced clearance, prolonged elimination half-life, and approximately doubled plasma levels of triazolam, hence increased clinical observation and consideration of dosage reduction may be appropriate. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No evidence of carcinogenic potential was observed in mice during a 24-month study with HALCION in doses up to 4000 times the human dose. *Pregnancy:* Benzodiazepines may cause fetal damage if administered during pregnancy. The child born of a mother who is on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity during the postnatal period. *Nursing Mothers:* Administration to nursing mothers is not recommended. *Pediatric Use:* Safety and efficacy in children below the age of 18 have not been established.

ADVERSE REACTIONS: During placebo-controlled clinical studies in which 1003 patients received HALCION Tablets, the most troublesome side effects were extensions of the pharmacologic activity of HALCION, e.g., drowsiness, dizziness, or lightheadedness.

	HALCION	Placebo
Number of Patients	1003	997
% of Patients Reporting:		
Central Nervous System		
Drowsiness	14.0	6.4
Headache	9.7	8.4
Dizziness	7.8	3.1
Nervousness	5.2	4.5
Lightheadedness	4.9	0.9
Coordination Disorder/Ataxia	4.6	0.8
Gastrointestinal		
Nausea/Vomiting	4.6	3.7

In addition, the following adverse events have been reported less frequently (i.e., 0.9-0.5%): euphoria, tachycardia, tiredness, confusional states/memory impairment, cramps/pain, depression, visual disturbances.

Rare (i.e., less than 0.5%) adverse reactions included constipation, taste alterations, diarrhea, dry mouth, dermatitis/allergy, dreaming/nightmares, insomnia, paresthesia, tinnitus, dysesthesia, weakness, congestion, death from hepatic failure in a patient also receiving diuretic drugs.

The following adverse events have been reported in association with the use of benzodiazepines: dystonia, irritability, anorexia, fatigue, sedation, slurred speech, jaundice, pruritus, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

As with all benzodiazepines, paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, hallucinations and other adverse behavioral effects may occur rarely and in a random fashion. Should these occur, use of the drug should be discontinued.

No laboratory changes were considered to be of physiological significance.

When treatment is protracted, periodic blood counts, urinalysis and blood chemistry analyses are advisable.

Minor changes in EEG patterns, usually low-voltage fast activity have been observed in patients during HALCION therapy and are of no known significance.

DRUG ABUSE AND DEPENDENCE: *Controlled Substance:* HALCION Tablets are a Controlled Substance in Schedule IV. *Abuse and Dependence:* Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Patients with a history of seizures are at particular risk. Addiction-prone patients should be closely monitored. Repeat prescriptions should be limited to those under medical supervision.

OVERDOSAGE: Because of the potency of triazolam, overdosage may occur at 2 mg, four times the maximum recommended therapeutic dose (0.5 mg). Manifestations of overdosage include somnolence, confusion, impaired coordination, slurred speech, and ultimately, coma. Respiration, pulse, and blood pressure should be monitored and supported by general measure when necessary. Immediate gastric lavage should be performed. Multiple agents may have been ingested.

Store at controlled room temperature 15°-30°C (59°-86°F).

Caution: Federal law prohibits dispensing without prescription. B-3-S

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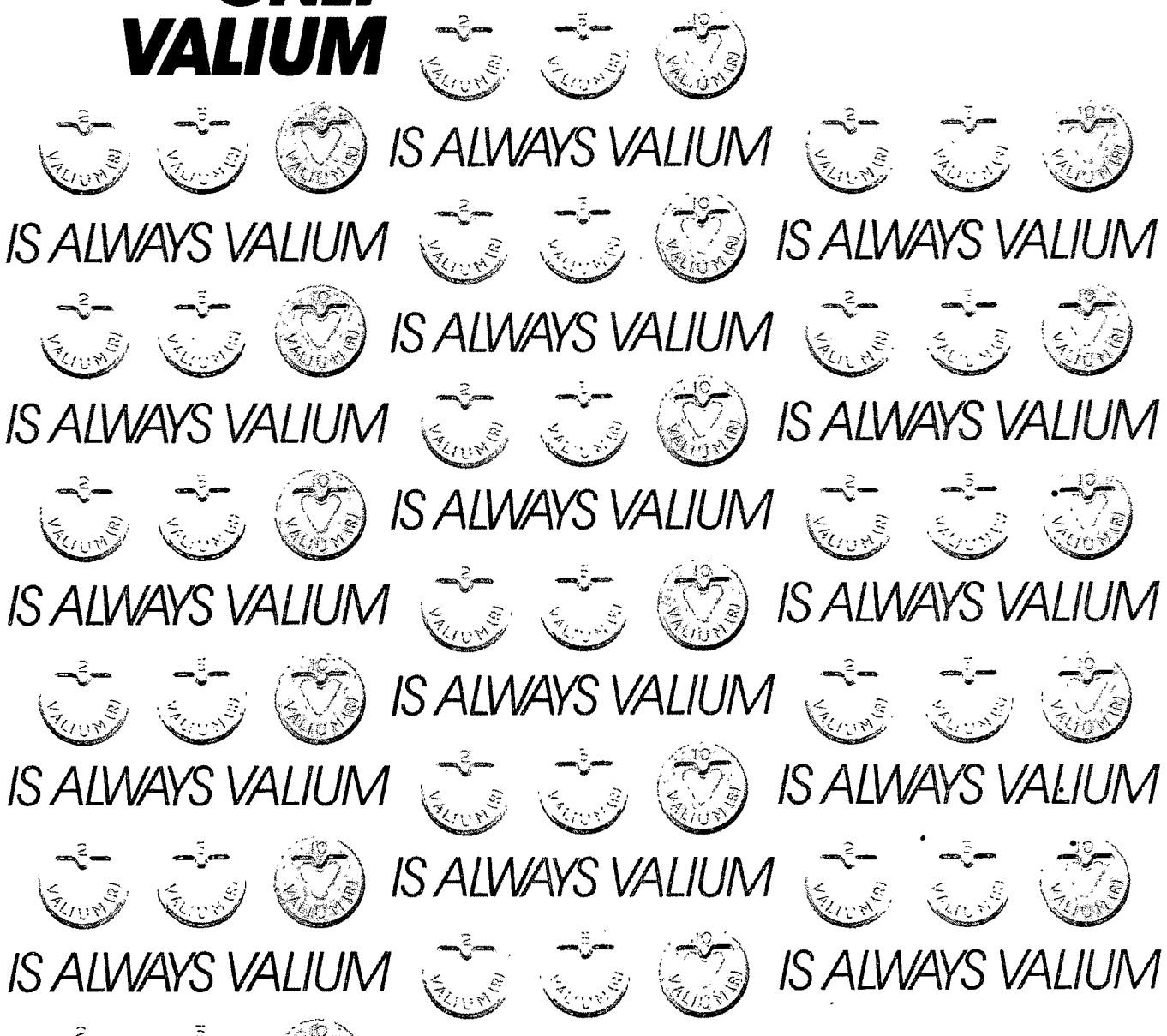
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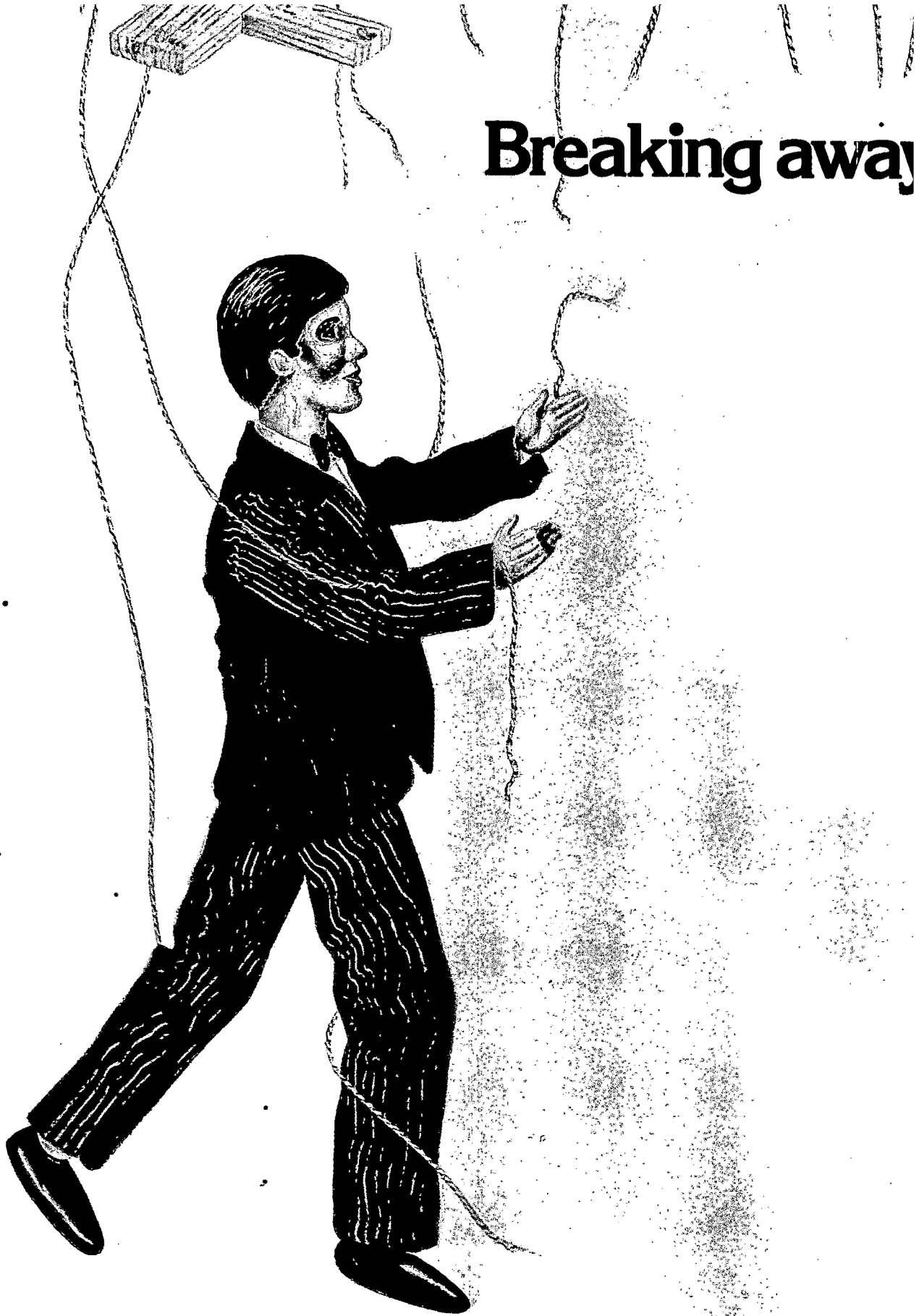
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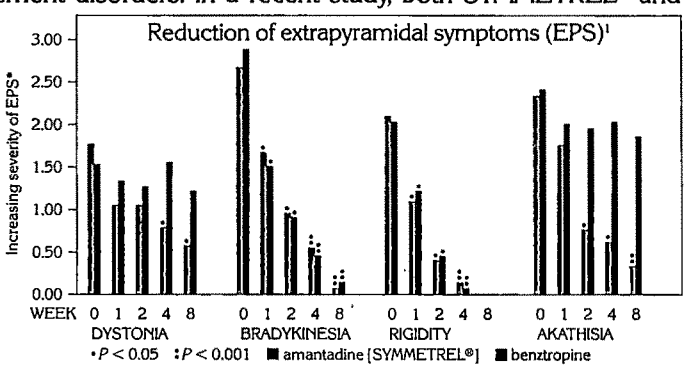


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*Extrapyramidal symptoms were rated on a four-point scale of ascending severity. —adapted from Borison and Diamond, p 42[1]

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Incidence of anticholinergic side effects[1]

	% patients taking amantadine	% patients taking benztropine
Dry mouth	7.4	41.6
Blurred vision	2.6	26.5
Nasal congestion	2.5	18.2
Constipation	1.8	21.4
Urinary hesitancy	1.3	7.1

—adapted from Borison and Diamond, p 43[1]

SYMMETREL®
100-MG CAPSULES
50 MG/5 ML SYRUP
(AMANTADINE HCl)

Please see following page for brief summary of prescribing information.

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(AMANTADINE HCl)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE: *Parkinson's Disease/Syndrome and Drug-Induced Extrapyramidal Reactions:* SYMMETREL is indicated in the treatment of idiopathic Parkinson's disease (Paralysis Agitans), postencephalitic parkinsonism, drug-induced extrapyramidal reactions, and symptomatic parkinsonism which may follow injury to the nervous system by carbon monoxide intoxication. It is indicated in those elderly patients believed to develop parkinsonism in association with cerebral arteriosclerosis. In the treatment of Parkinson's disease, SYMMETREL is less effective than levodopa, (-)-3-(3, 4-dihydroxyphenyl)-L-alanine, and its efficacy in comparison with the anticholinergic antiparkinson drugs has not yet been established. Although anticholinergic type side effects have been noted with SYMMETREL when used in patients with drug-induced extrapyramidal reactions, there is a lower incidence of these side effects than that observed with anticholinergic antiparkinson drugs.

CONTRAINDICATIONS: SYMMETREL is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS: Patients with a history of epilepsy or other "seizures" should be observed closely for possible increased seizure activity.

Patients with a history of congestive heart failure or peripheral edema should be followed closely as there are patients who developed congestive heart failure while receiving SYMMETREL.

Patients with Parkinson's disease improving on SYMMETREL should resume normal activities gradually and cautiously, consistent with other medical considerations, such as the presence of osteoporosis or phlebothrombosis.

Patients receiving SYMMETREL who note central nervous system effects or blurring of vision should be cautioned against driving or working in situations where alertness is important.

PRECAUTIONS: SYMMETREL (amantadine hydrochloride) should not be discontinued abruptly since a few patients with Parkinson's disease experienced a parkinsonian crisis, i.e., a sudden marked clinical deterioration, when this medication was suddenly stopped. The dose of anticholinergic drugs or of SYMMETREL should be reduced if atropine-like effects appear when these drugs are used concurrently.

The dose of SYMMETREL may need careful adjustment in patients with renal impairment, congestive heart failure, peripheral edema, or orthostatic hypotension. Since SYMMETREL is not metabolized and is mainly excreted in the urine, it may accumulate when renal function is inadequate.

Care should be exercised when administering SYMMETREL to patients with liver disease, a history of recurrent eczematoid rash, or to patients with psychosis or severe psychoneurosis not controlled by chemotherapeutic agents. Careful observation is required when SYMMETREL is administered concurrently with central nervous system stimulants.

No long-term studies in animals have been performed to evaluate the carcinogenic potential of SYMMETREL. The mutagenic potential of the drug has not yet been determined in experimental systems.

Pregnancy Category C: SYMMETREL (amantadine hydrochloride) has been shown to be embryotoxic and teratogenic in rats at 50 mg/kg/day, about 12 times the recommended human dose, but not at 37 mg/kg/day. Embryotoxic and teratogenic drug effects were not seen in rabbits which received up to 25 times the recommended human dose. There are no adequate and well-controlled studies in pregnant women.

SYMMETREL should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or the fetus.

Nursing Mothers: SYMMETREL is excreted in human milk. Caution should be exercised when SYMMETREL is administered to a nursing woman.

Pediatric Use: The safety and efficacy of SYMMETREL in newborn infants, and infants below the age of 1 year have not been established.

ADVERSE REACTIONS: The most frequently occurring serious adverse reactions are: depression, congestive heart failure, orthostatic hypotensive episodes, psychosis, and urinary retention. Rarely convulsions, leukopenia, and neutropenia have been reported.

Other adverse reactions of a less serious nature which have been observed are the following: hallucinations, confusion, anxiety; irritability; anorexia, nausea, and constipation; ataxia and dizziness (lightheadedness); livedo reticularis and peripheral edema. Adverse reactions observed less frequently are the following: vomiting; dry mouth; headache; dyspnea; fatigue, insomnia, and a sense of weakness. Infrequently, skin rash, slurred speech, and visual disturbances have been observed. Rarely eczematoid dermatitis and oculogyric episodes have been reported.

DOSAGE AND ADMINISTRATION: Adult Dosage for Parkinsonism: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day when used alone. SYMMETREL has an onset of action usually within 48 hours.

The initial dose of SYMMETREL is 100 mg daily for patients with serious associated medical illnesses or who are receiving high doses of other antiparkinson drugs. After one to several weeks at 100 mg once daily, the dose may be increased to 100 mg twice daily, if necessary.

Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 400 mg daily in divided doses. However, such patients should be supervised closely by their physicians.

Patients initially deriving benefit from SYMMETREL not uncommonly experience a fall-off of effectiveness after a few months. Benefit may be regained by increasing the dose to 300 mg daily. Alternatively, temporary discontinuation of SYMMETREL for several weeks, followed by reinitiation of the drug, may result in regaining benefit in some patients. A decision to use other antiparkinson drugs may be necessary.

Dosage for Concomitant Therapy: Some patients who do not respond to anticholinergic antiparkinson drugs may respond to SYMMETREL. When SYMMETREL or anticholinergic antiparkinson drugs are each used with marginal benefit, concomitant use may produce additional benefit.

When SYMMETREL and levodopa are initiated concurrently, the patient can exhibit rapid therapeutic benefits. SYMMETREL should be held constant at 100 mg daily or twice daily while the daily dose of levodopa is gradually increased to optimal benefit.

When SYMMETREL is added to optimal well-tolerated doses of levodopa, additional benefit may result, including smoothing out the fluctuations in improvement which sometimes occur in patients on levodopa alone. Patients who require a reduction in their usual dose of levodopa because of the development of side effects may possibly regain lost benefit with the addition of SYMMETREL.

Dosage for Drug-Induced Extrapyramidal Reactions: Adult: The usual dose of SYMMETREL (amantadine hydrochloride) is 100 mg twice a day. Occasionally, patients whose responses are not optimal with SYMMETREL at 200 mg daily may benefit from an increase up to 300 mg daily in divided doses. 6043-15BSP/Rev. Oct. 1984

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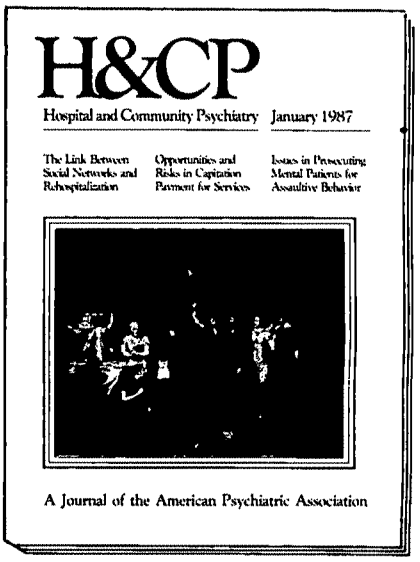
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REFERENCE: 1. Borison RL, Diamond BI: Treatment of extrapyramidal side-effects: Amantadine versus benztropine. *World J Psychosynthesis* (special), 1984-1985, pp 40-43.

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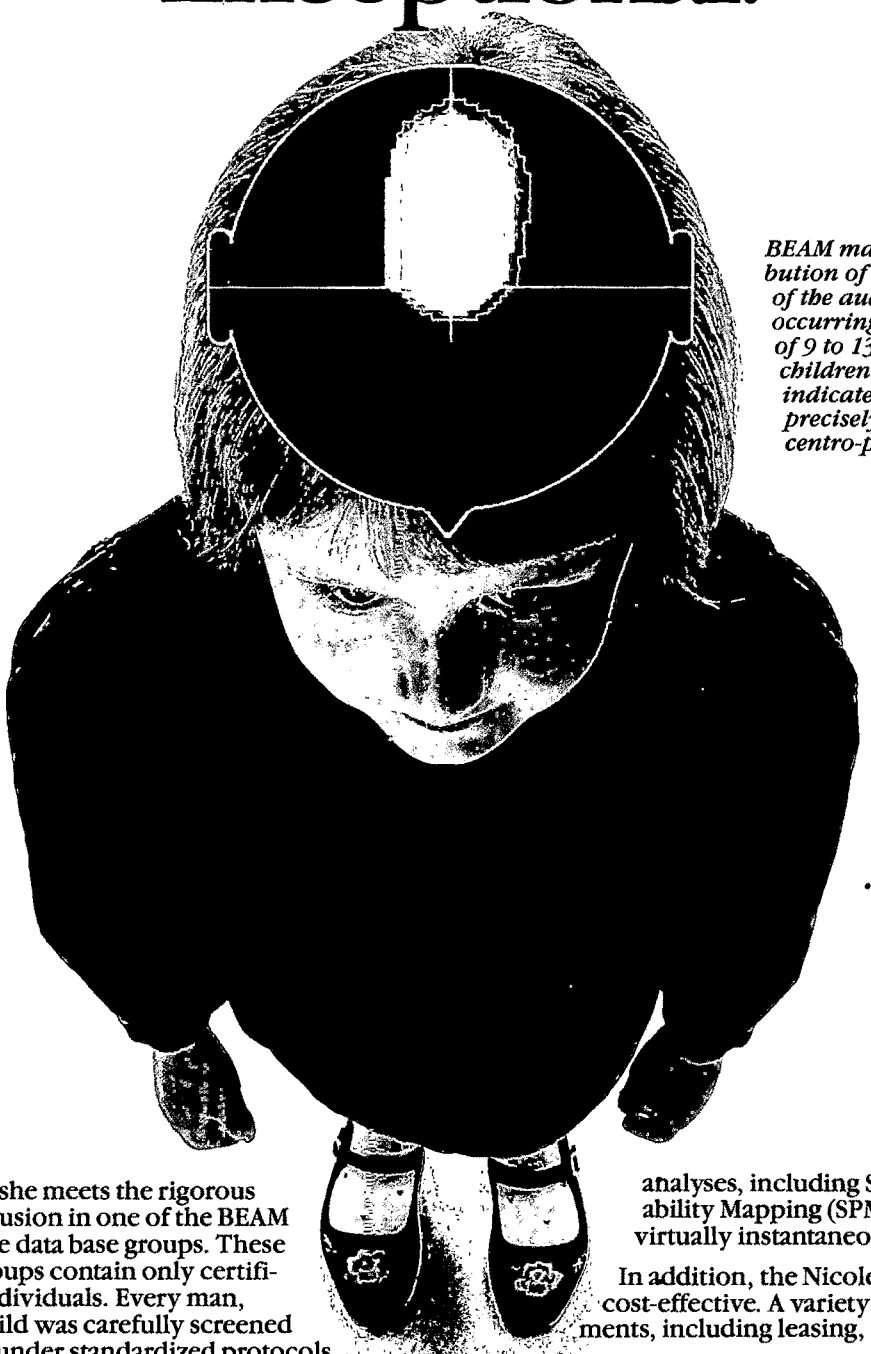
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Nicolet
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Calendar

(Continued from page A24)

Chief Administrative Officer, 225 Lisgar St., Suite 103, Ottawa, Ontario K2P 0C6, Canada; 613-234-2815.

September 16–20, annual convention, National Alliance for the Mentally Ill, Washington, D.C. Contact NAMI, 1901 North Ft. Myer Dr., Suite 500, Arlington, VA 22209; 703-524-7600.

September 17–18, semiannual meeting, American Board of Medical Specialties, Chicago. Contact Donald G. Langsley, M.D., Executive Vice-President, One American Plaza, Suite 805, Evanston, IL 60201; 312-491-9091.

September 18–20, child psychiatry examination, American Board of Psychiatry and Neurology, Minneapolis. Contact Stephen C. Scheiber, M.D., Executive Secretary, One American Plaza, Suite 808, Evanston, IL 60201; 312-846-0830.

September 22–25, International Symposium, Brain Acetylcholine: From Preclinical to Clinical Investigations, Taormina, Italy. Contact A.P. Caputi, M.D., Institute of Pharmacology, University of Messina, Piazza XX Settembre, 4, 98100 MESSINA (Italy); 090-712533.

September 22–27, VIIIth European Congress of Child and Adolescent Psychiatry, Varna, Bulgaria. Contact Prof. Dr. Chr. Christosov, Dept. of Psychiatry, Medical Academy, Sofia, 1431, Bulgaria.

September 24–October 1, II Annual Conference on the Foundations of Behavioral Neurology, Hong Kong. Contact Teresa Santana, Assistant Program Director, So. California Neuropsychiatric Institute, 6794 La Jolla Blvd., La Jolla, CA 92037; 619-454-2121, 800-423-9521.

September 26–29, annual meeting, Southern Psychiatric Association, Boca Raton, Fla. Contact Annette S. Boutwell, Executive Director, P.O. Box 10387, Raleigh, NC 27605; 919-821-2226.

September 27–30, annual meeting, Association of Mental Health Administrators, Hollywood, Fla. Contact Weir Richard Kirk, Executive Director, 840 North Lake Shore Dr., Suite 1103W, Chicago, IL 60611; 312-943-2751.

September 27–October 2, annual meeting, American Health Care Association, New York. Contact Paul R. Willging, Ph.D., Executive Director, 1200 15th St., N.W., 8th Fl., Washington, DC 20005-2899; 202-833-2050.

September 28–October 3, annual meeting, Pan American Health Organization, Washington, D.C. Contact Carlyle Guerra de Macedo, M.D., Director, 525 23rd St., N.W., Washington, DC 20037; 202-861-3200.

OCTOBER

October 6–11, annual meeting, American School Health Association, Indianapolis. Contact Dana A. Davis, Executive Director, P.O. Box 708, Kent, OH 44240; 216-678-1601.

October 7–10, annual meeting, American Academy for Cerebral Palsy and Developmental Medicine, Boston. Contact John A. Hinckley, Executive Director, P.O. Box 11083, Richmond, VA 23230; 804-355-0147.

October 7–10, annual meeting, American Academy of Clinical Psychiatrists, Toronto. Contact Robert Budetti, Executive Secretary, P.O. Box 3212, San Diego, CA 92103; 619-460-2675.

October 8–11, annual meeting, American Medical Care and Review Association, Monterey, Calif. Contact Ronald A. Hurst, Executive Vice-President, 5410 Grosvenor Ln., Suite 210, Bethesda, MD 20814; 301-493-9552.

October 9–12, Vth Scientific Conference of the International Federation of Psychoanalytic Societies, New York. Contact Ann R. Turkel, M.D., Secretary-General of the IFPS, 350 Central Park West, New York, NY 10025; 212-831-3400.

October 11–16, annual meeting, American College of Surgeons, San Francisco. Contact C. Rollins Hanlon, M.D., F.A.C.S., Executive Director, 55 East Erie St., Chicago, IL 60610; 312-664-4050.

October 15–17, annual meeting, Canadian Association for Community Living, Washington, D.C. Contact Jacques Peletier, Executive Vice-President, Kinsmen Bldg., York University Campus, 4700 Keele St., Downsview, Ontario M3J 1P3, Canada; 416-661-9600.

October 15–17, annual conference, Canadian Group Psychotherapy Association, Banff, Alberta, Canada. Contact Dr. Edgardo Perez, Dept. of Psychiatry, Ottawa Civic Hospital, 1053 Carling Ave., Ottawa, Ontario K1Y 4E9, Canada.

October 15–17, annual meeting, National Association for Retarded Citizens, Washington, D.C. Contact Alan Abeson, Ed.D., Executive Director, 2501 Avenue "J," Arlington, TX 76006; 817-640-0204.

October 15–18, annual meeting, American Academy of Psychiatry and the Law, Ottawa. Contact Ms. Kathy Smith, AAPL, 1211 Cathedral St., Baltimore, MD 21201; 301-539-0379.

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Xanax® 0.5 mg Tablets
alprazolam C-IV

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A UNIQUE STRUCTURE TO SUPPORT YOUR PSYCHOTHERAPY.



Xanax® 0.5 mg Tablets
alprazolam C IV

XANAX® Tablets
(alprazolam) C IV

CONTRAINDICATIONS
Patients with sensitivity to this drug or other benzodiazepines and in acute narrow angle glaucoma.

WARNINGS
Not of value in psychotic patients. Caution patients against hazardous occupations requiring complete mental alertness and about the simultaneous ingestion of alcohol and other CNS depressant drugs.

Benzodiazepines can cause fetal harm in pregnant women. Warn patients of the potential hazard to the fetus. Avoid during the first trimester.

PRECAUTIONS
General: The dosage of XANAX Tablets should be reduced or withdrawn gradually, since withdrawal seizures have been reported upon abrupt withdrawal. If XANAX is combined with other psychotropics or anticonvulsant drugs, consider drug potentiation (see Drug Interaction section). Exercise the usual precautions regarding size of the prescription for depressed or suicidal patients. In elderly and debilitated patients, use the lowest possible dosage (see Dosage and Administration). Observe the usual precautions in treating patients with impaired renal or hepatic function.

Information for Patients: Alert patients about: (a) consumption of alcohol and drugs, (b) possible fetal abnormalities, (c) operating machinery or driving, (d) not increasing dose of the drug due to risk of dependence, (e) not stopping the drug abruptly. *Laboratory Tests:* Not ordinarily required in otherwise healthy patients. *Drug Interactions:* Additive CNS depressant effects with other psychotropics, anticonvulsants, antihistamines, ethanol and other CNS depressants. Pharmacokinetic interactions with benzodiazepines have been reported. *Drug/Laboratory Test Interactions:* No consistent pattern for a specific drug or specific test. *Carcinogenesis, Mutagenesis, Impairment of Fertility:* No carcinogenic potential or impairment of fertility in rats. *Pregnancy:* See Warnings. *Nonteratogenic Effects:* The child born of a mother on benzodiazepines may be at some risk for withdrawal symptoms and neonatal flaccidity. *Labor and Delivery:* No established use. *Nursing Mothers:* Benzodiazepines are excreted in human milk. Women on XANAX should not nurse. *Pediatric Use:* Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS
Side effects are generally observed at the beginning of therapy and usually disappear with continued medication. In the usual patient, the most frequent side effects are likely to be an extension of the pharmacologic activity of XANAX, eg, drowsiness or lightheadedness.

Central nervous system. Drowsiness, lightheadedness, depression, headache, confusion, insomnia, nervousness, syncope, dizziness, akathisia, and tiredness/sleepiness.

Gastrointestinal: Dry mouth, constipation, diarrhea, nausea/vomiting, and increased salivation.

Cardiovascular: Tachycardia/palpitations, and hypotension.

Sensory: Blurred vision.

Musculoskeletal: Rigidity and tremor.

Cutaneous: Dermatitis/allergy.

Other side effects: Nasal congestion, weight gain, and weight loss.

In addition, the following adverse events have been reported with the use of benzodiazepines: dystonia, irritability, concentration difficulties, anorexia, transient amnesia or memory impairment, loss of coordination, fatigue, sedation, slurred speech, jaundice, musculoskeletal weakness, pruritus, diplopia, dysarthria, changes in libido, menstrual irregularities, incontinence and urinary retention.

Paradoxical reactions such as stimulation, agitation, increased muscle spasticity, sleep disturbances, and hallucinations may occur. Should these occur, discontinue the drug.

During prolonged treatment, periodic blood counts, urinalysis, and blood chemistry analysis are advisable. Minor EEG changes of unknown significance have been observed.

DRUG ABUSE AND DEPENDENCE
Physical and Psychological Dependence: Withdrawal symptoms have occurred following abrupt discontinuance of benzodiazepines. Withdrawal seizures have occurred upon rapid decrease or abrupt discontinuation of therapy. In all patients, dosage should be gradually tapered under close supervision. Patients with a history of seizures or epilepsy should not be abruptly withdrawn from XANAX. Addiction-prone individuals should be under careful surveillance. *Controlled Substance Class:* XANAX is a controlled substance and has been assigned to schedule IV.

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B-4-S
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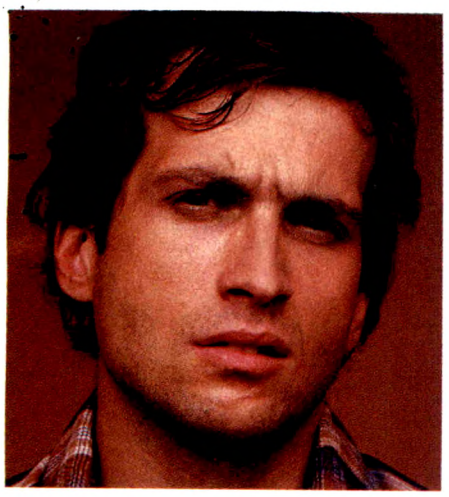
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The following is a brief summary only. Before prescribing, see complete prescribing information in HALDOL and HALDOL Decanoate product labeling.

Contraindications: Since the pharmacologic and clinical actions of HALDOL (haloperidol) Decanoate are attributed to HALDOL as the active medication, Contraindications, Warnings, and additional information are those of HALDOL. Some sections have been modified to reflect the prolonged action of HALDOL Decanoate.

HALDOL is contraindicated in severe toxic central nervous system depression or comatose states from any cause and in individuals who are hypersensitive to this drug or have Parkinson's disease.

Warnings: *Tardive Dyskinesia:* Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. Both the risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, antipsychotic drugs should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that 1) is known to respond to antipsychotic drugs, and 2) for whom alternative, equally effective, but potentially less harmful treatments are **not** available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on antipsychotics, drug discontinuation should be considered. However, some patients may require treatment despite the presence of the syndrome. (For further information about the description of tardive dyskinesia and its clinical detection, please refer to ADVERSE REACTIONS.)

Usage in Pregnancy: (see PRECAUTIONS - Usage in Pregnancy) *Combined Use With Lithium:* (see PRECAUTIONS - Drug Interactions).

General: Bronchopneumonia, sometimes fatal, has followed use of antipsychotic drugs, including haloperidol. Prompt remedial therapy should be instituted if dehydration, hemoconcentration or reduced pulmonary ventilation occur, especially in the elderly. Decreased serum cholesterol and/or cutaneous and ocular changes have been reported with chemically-related drugs, although not with haloperidol. See PRECAUTIONS - Information for Patients for information on mental and/or physical abilities and on concomitant use with other substances.

Precautions: Administer cautiously to patients: (1) with severe cardiovascular disorders, due to the possibility of transient hypotension and/or precipitation of anginal pain (if a vasopressor is required, epinephrine should not be used since HALDOL may block its vasopressor activity and paradoxical further lowering of blood pressure may occur; metaraminol, phenylephrine or norepinephrine should be used); (2) receiving anticonvulsant medications, with a history of seizures, or with EEG abnormalities, because HALDOL may lower the convulsive threshold. If indicated, adequate anticonvulsant therapy should be concomitantly maintained; (3) with known allergies or a history of allergic reactions to drugs; (4) receiving anticoagulants, since an isolated instance of interference occurred with the effects of one anticoagulant (phenindione). Concomitant antiparkinson medication, if required, may have to be continued after HALDOL is discontinued because of different excretion rates; if both are discontinued simultaneously, extrapyramidal symptoms may occur. Intraocular pressure may increase when anticholinergic drugs, including antiparkinson drugs, are administered concomitantly with HALDOL. When HALDOL is used for mania in bipolar disorders, there may be a rapid mood swing to depression. Severe neurotoxicity may occur in patients with thyrotoxicosis receiving antipsychotic medication, including HALDOL.

The 1, 5 and 10 mg HALDOL tablets contain FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible individuals, especially in those who have aspirin hypersensitivity.

Information for Patients: Mental and/or physical abilities required for hazardous tasks or driving may be impaired. Alcohol should be avoided due to possible additive effects and hypotension.

Drug Interactions: Patients receiving lithium plus haloperidol should be monitored closely for early evidence of neurological toxicity and treatment discontinued promptly if such signs appear.

Carcinogenesis, Mutagenesis and Impairment of Fertility: No mutagenic potential of haloperidol decanoate was found in the Ames Salmonella microsomal activation assay.

Carcinogenicity studies using oral haloperidol were conducted in Wistar rats (dosed at up to 5 mg/kg daily for 24 months) and in Albino Swiss mice (dosed at up to 5 mg/kg daily for 18 months). In the rat study survival was less than optimal in all dose groups, reducing the number of rats at risk for developing tumors. However, although a relatively greater number of rats survived to the end of the study in high dose male and female groups, these animals did not have a greater incidence of tumors than control animals. Therefore, although not optimal, this study does suggest the absence of a haloperidol related increase in the incidence of neoplasia in rats at doses up to 20 times the usual daily human dose for chronic or resistant patients. In female mice at 5 and 20 times the highest initial daily dose for chronic or resistant patients, there was a statistically significant increase in mammary gland neoplasia and total tumor incidence; at 20 times the same daily dose there was a statistically significant increase in pituitary gland neoplasia. In male mice, no statistically significant differences in incidences of total tumors or specific tumor types were noted.

Antipsychotic drugs elevate prolactin levels; the elevation persists during chronic administration. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with a previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported, the clinical significance of elevated serum prolactin levels is unknown for most patients. An increase in mammary neoplasms has been found in rodents after chronic administration of antipsychotic drugs. Neither clinical studies nor epidemiologic studies conducted to date, however, have shown an association between chronic administration of these drugs and mammary tumorigenesis: the available evidence is considered too limited to be conclusive at this time.

Usage in Pregnancy: Pregnancy Category C. Safe use in pregnancy or in women likely to become pregnant has not been established; use only if benefit clearly justifies potential hazards to the fetus.

Nursing Mothers: Infants should not be nursed during drug treatment.

Pediatric Use: Controlled trials to establish the safety and effectiveness of intramuscular administration in children have not been conducted.

Adverse Reactions: Adverse reactions following the administration of HALDOL (haloperidol) Decanoate are those of HALDOL. Since vast experience has accumulated with HALDOL, the adverse reactions are reported for that compound as well as for HALDOL Decanoate. As with all injectable medications, local tissue reactions have been reported with HALDOL Decanoate.

CNS Effects: Extrapyramidal Reactions: Neuromuscular (extrapyramidal) reactions have been reported frequently, often during the first few days of treatment. Generally they involved Parkinson-like symptoms which when first observed were usually mild to moderately severe and usually reversible. Other types of neuromuscular reactions (motor restlessness, dystonia and tardive dystonia, akathisia, hyperreflexia, opisthotonos, oculogyric crises) have been reported far less frequently, but were often more severe. Severe extrapyramidal reactions have been reported at relatively low doses. Generally, extrapyramidal symptoms are dose-related since they occur at relatively high doses and disappear or become less severe when the dose is reduced. Antiparkinson drugs may be required. Persistent extrapyramidal reactions have been reported and the drug may have to be discontinued in such cases. *Withdrawal Emergent Neurological Signs*—Abrupt discontinuation of short-term antipsychotic therapy is generally uneventful. However, some patients on maintenance treatment experience transient dyskinetic signs after abrupt withdrawal. In certain cases these are indistinguishable from "Tardive Dyskinesia" except for duration. It is unknown whether gradual withdrawal will reduce the occurrence of these signs, but until further evidence is available HALDOL should be gradually withdrawn. *Tardive Dyskinesia*—As with all antipsychotic agents HALDOL has been associated with persistent dyskinesias. Tardive dyskinesia, a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements, may appear in some patients on long-term therapy or may occur after drug therapy has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. The symptoms are persistent and in some patients appear irreversible. The syndrome is characterized by rhythmical involuntary movements of tongue, face, mouth or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Sometimes these may be accompanied by involuntary movements of extremities and the trunk. There is no known effective treatment for tardive dyskinesia; antiparkinson agents usually do not alleviate the symptoms of this syndrome. It is suggested that all antipsychotic agents be discontinued if these symptoms appear. Should it be necessary to reinstitute treatment, or increase the dosage of the agent, or switch to a different antipsychotic agent, this syndrome may be masked. It has been reported that fine vermicular movement of the tongue may be an early sign of tardive dyskinesia and if the medication is stopped at that time the syndrome may not develop. *Other CNS Effects*—Insomnia, restlessness, anxiety, euphoria, agitation, drowsiness, depression, lethargy, headache, confusion, vertigo, grand mal seizures, and exacerbation of psychotic symptoms including hallucinations, and catatonic-like behavioral states which may be responsive to drug withdrawal and/or treatment with anticholinergic drugs.

Body as a Whole: Neuroleptic Malignant Syndrome: As with other antipsychotic drugs, a symptom complex sometimes referred to as neuroleptic malignant syndrome (NMS) has been reported. Cardinal features of NMS are hyperpyrexia, muscle rigidity, altered mental status (including catatonic signs), and evidence of autonomic instability (irregular pulse or blood pressure). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. NMS is potentially fatal, requires intensive symptomatic treatment and immediate discontinuation of antipsychotic treatment. Hyperpyrexia and heat stroke, not associated with the above symptom complex, have also been reported. *Cardiovascular Effects:* Tachycardia, hypotension, hypertension and ECG changes. *Hematologic Effects:* Reports of mild, usually transient leukopenia and leukocytosis, minimal decreases in red blood cell counts, anemia, or a tendency toward lymphomonocytosis; agranulocytosis rarely reported and only in association with other medication. *Liver Effects:* Impaired liver function and/or jaundice. *Dermatologic Reactions:* Maculopapular and acneiform reactions, isolated cases of photosensitivity, loss of hair. *Endocrine Disorders:* Lactation, breast engorgement, mastalgia, menstrual irregularities, gynecomastia, impotence, increased libido, hyperglycemia, hypoglycemia and hyponatremia. *Gastrointestinal Effects:* Anorexia, constipation, diarrhea, hypersalivation, dyspepsia, nausea and vomiting. *Autonomic Reactions:* Dry mouth, blurred vision, urinary retention, diaphoresis, and priapism. *Respiratory Effects:* Laryngospasm, bronchospasm and increased depth of respiration. *Special Senses:* Cataracts, retinopathy and visual disturbances. *Other:* Cases of sudden and unexpected death have been reported in association with the administration of HALDOL. The nature of the evidence makes it impossible to determine definitively what role, if any, HALDOL played in the outcome of the reported cases. The possibility that HALDOL caused death cannot, of course, be excluded, but it is to be kept in mind that sudden and unexpected death may occur in psychotic patients when they go untreated or when they are treated with other antipsychotic drugs.

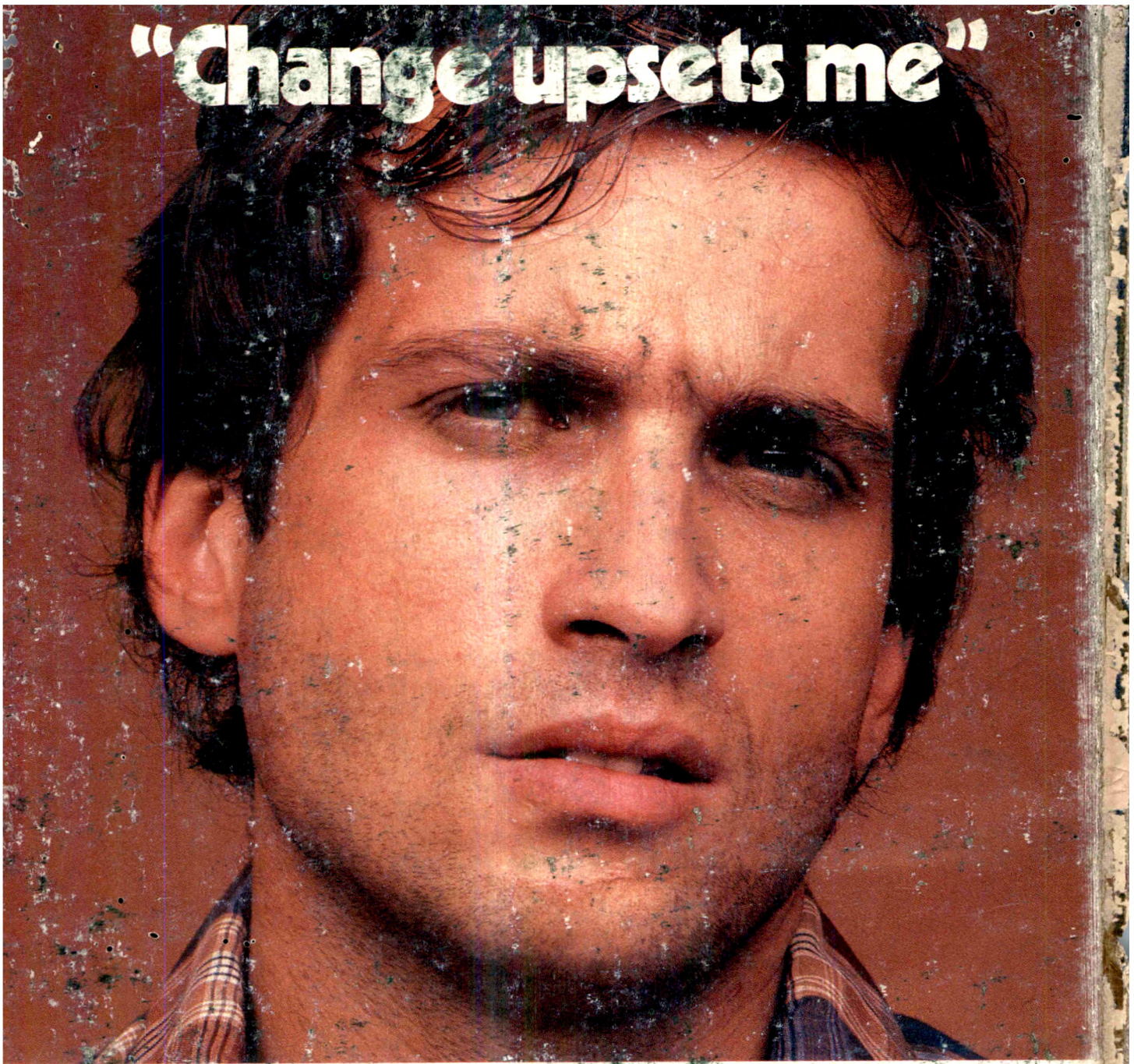
IMPORTANT: Full directions for use should be read before HALDOL or HALDOL Decanoate is administered or prescribed. For information on symptoms and treatment of overdosage, see full prescribing information.

The short-acting HALDOL injectable form is intended only for acutely agitated psychotic patients with moderately severe to very severe symptoms.

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*Emphasis added.

1. Grinspoon L (ed): Care and treatment of schizoprenia – Part II, in *The Harvard Medical School Mental Health Letter* 1986, 3(1): 1.

Patient portrayed by professional model.

Please see brief summary of Prescribing Information on the preceding page.

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